ANTIARRHYTHMIC ACTIVITY OF ANTAZOLINE AND ITS APPLICATION TO THE CONTROL OF HYPOTHERMIC VENTRICULAR FIBRILLATION

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FOREWORD

This study was initiated by the Biomedical Laboratory of the Aerospace Medical Research Laboratories, Aerospace Medical Division, Wright-Patterson Air Force Base, Ohio. The research was conducted in the Hypothermia Laboratory at the Department of Physiology of Boston University School of Medicine under Contract No. AF 33(657)-10755. Dr. E.T. Angelakos was the principal investigator for Boston University School of Medicine. Mr. J.F. Hall, Jr., Chief of the Biothermal Branch, was the contract monitor for the Aerospace Medical Research Laboratories. The work was begun in support of Project No. 7222 "Biophysics in Flight" and Task No. 722204 "Human Thermal Stress in Extended Environment" and was continued under Project No. 7164 "Biomedical Criteria for Aerospace Flight" and Task No. 716409 "Human Thermal Stress." This report covers research performed between February 1963 and April 1965.

This technical report has been reviewed and is approved.

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ABSTRACT

The chemistry and general pharmacology of antazoline and experimental studies employing it are reviewed to determine the antiarrhythmic activity and the protective effect of antazoline against hypothermic ventricular fibrillation. In hypothermic ventricular fibrillation and in clinically observed heart disorders, the antiarrhythmic activity of antazoline was often superior to other pharmacological agents, including quinidine. The incidence of side effects, notably nausea or vomiting, was found to be related to the dosage. Since the basis of the antiarrhythmic activity of antazoline is essentially unknown, further studies in this direction are warranted to provide for systematic development of more effective compounds.

I. INTRODUCTION.

It is now well known that survival in acute hypothermia in man and many animals is limited by the development of lethal ventricular fibrillation at relatively high body temperatures at a time when all other functions and the general cardiovascular status are adequate. This phenomenon has been studied most extensively in man and in the dog and the available information has been summarized (1,2)*. In general, it can be shown that if the development of hypothermic ventricular fibrillation can be prevented, survival can be extended to much lower body temperatures. The incidence of spontaneous hypothermic ventricular fibrillation can be reduced by controlling blood pH (3) and calcium ion concentration (4). However, for practical purposes, in cases of accidental exposure to cold and development of hypothermia, the only effective means for prolonging life at lower body temperatures would be the availability of a pharmacological agent which is orally effective and which can prevent the development of lethal hypothermic ventricular fibrillation.

In a series of studies made in this laboratory between 1957 and 1959 by Angelakos, Hegnauer and their associates (5 thru 8), a large number of compounds (over 200) were screened regarding their ability to protect from the development of hypothermic ventricular fibrillation.

In these studies of the well-known antiarrhythmics, quinidine was found to be moderately effective against spontaneous hypothermic ventricular fibrillation while procaine amide was shown to be totally ineffective. Among all other compounds tested only antazoline, a known antihistaminic drug, was found to have a potency superior to that of quinidine in preventing hypothermic ventricular fibrillation. It appeared, therefore, that antazoline could provide the answer to the question under study since it is known that it can be taken orally and that, like other antihistaminics, its acute toxicity is rather low.

Since these experiments were performed on dogs, it remained to be shown whether antazoline was equally effective on man.

In the case of quinidine, there was little doubt that the findings in the dog would be applicable in man since this compound was known to be effective against a variety of other arrhythmias in man. In this case, the results in the dog indicated that

* See reference section at end of report.

quinidine was effective in the particular conditions which prevail in hypothermic ventricular fibrillation, which in all probability are quite similar in both man and dog.

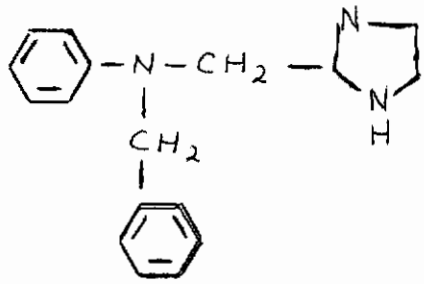
However, in the case of antazoline, no information was available that this compound had any antiarrhythmic activity in man. Therefore, when the experimental studies were completed it was not established whether a compound which was effective in hypothermic ventricular fibrillation in man was indeed discovered.

In the past five years, prompted by the observations of Angelakos and Hegnauer on the effectiveness of antazoline in preventing hypothermic ventricular fibrillation, a number of clinical reports appeared indicating that antazoline is indeed effective against a variety of arrhythmias in man. Furthermore, the initial experimental observations have been confirmed by others and extended in studies where antazoline was tested against other experimental arrhythmias.

The purpose of this report is to review the basic pharmacology of antazoline and to summarize the available evidence of its antiarrhythmic activity in experimental and clinical arrhythmias. This review was completed in December, 1964.

II. CHEMISTRY.

Chemically antazoline is 2-(N-phenyl-N-benzyl-aminomethyl)-2-imidazoline. It is also known as imidamine, phenazoline and under several trade names including Antistine, Antistin, Histostab, Antastan, Antasten, Antihistal, Ben-a-hist and compound #5512-M. Its chemical formula is shown below:



From its chemical structure it is immediately apparent that antazoline is an analog of the earliest antihistaminic, antergan. It differs from antergan in that the nitrogen in the side chain of antazoline is incorporated into an imidazole ring. It was initially prepared by Miescher, Urech and Klarer (9) and first studied pharmacologically by Meier and Bucher (10).

Its chemical composition is $C_{17}H_{19}N_3$ and has a molecular weight of 265.35. It exists as crystals of the free base, the hydrochloride (HCl) or the phosphate (H_3PO_4), all having a bitter taste. Both the phosphate and hydrochloride are soluble in water but practically insoluble in ether, benzene or chloroform. A 1% solution of the hydrochloride has a pH of 6.3 while a 2% solution of the phosphate has a pH of 4.5.

No chemical methods have been published for the determination of antazoline in body fluids and tissues. Since the compound is an imidazoline, it is possible that available photometric and fluorometric methods for the detection of this class of compounds could be applied to the determination of antazoline.

III. PHARMACOLOGY.

In this section the antihistaminic activity, related pharmacological properties and toxicity of antazoline are reviewed. The antiarrhythmic activity and other cardiovascular effects are presented in separate subsequent sections (IV and V).

A. Antihistaminic activity:

The activity of antazoline as an antihistaminic has been studied extensively in the original studies of Meier and Bucher (10) and later by Graham (12), Reuse (13), and Craver et al. (14,15).

According to these reports, antazoline appears to share with other antihistamines the ability to antagonize most of the pharmacological effects of histamine (including smooth muscle contraction and vasodilation), with the notable exception of the effect of histamine in increasing gastric acid secretion.

Graham (12) reported that in histamine induced bronchospasm in the guinea pig, antazoline was about 1/2 as active as Benadryl* (diphenhydramine) and about 1/4 as active as Neoantergan* (pyrilamine). In histamine induced hypotension in the cat, antazoline was found by this worker to be about nine times less effective than Neoantergan*. In intestinal smooth muscle antazoline was about fifty times less potent than Neoantergan and twenty-five times less potent than Benadryl. Similar results regarding antihistaminic potency were reported by Reuse. (13)

A summary of some of the antihistaminic properties of antazoline as compared to those of other antihistaminics and especially to Antergan*, Benadryl*, Pyribenzamine* and Neoantergan* is given in a review by Loew (19).

Unfortunately, most of these comparisons are based on potency ratios, i.e. comparison of doses which produce an equal degree of antagonism. As such they reflect the degree of affinity of the antagonist for the histamine "receptor" but do not give a conclusive indication of the overall potency of each compound at maximum dose levels.

In any event it appears that as an antihistaminic, antazoline has low potency as compared to other available compounds of the same class. This perhaps accounts for the rather limited clinical use of antazoline as an antihistamine at the present time.

Early studies on the use of antazoline in dermatological disorders with allergic background were reported by Brack (15). In more recent years the clinical application of antazoline has been limited to its use as an ophthalmic ointment for certain allergic reactions of the eye (17). This use is apparently related to clinical reports of antazoline being milder and less irritating to tissues than other antihistaminics. In the eye it is said to produce less stinging than other antihistaminic preparations. In this application, 0.5% isotonic solution of antazoline phosphate is used.

B. Other pharmacological effects.

Like other antihistaminics, antazoline possesses a number of pharmacological activities which are apparently not related to its antihistaminic properties (19) but are nevertheless common

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*The trade names of these compounds are given here since, to most readers, they are more familiar than the accepted generic names. The latter are given in parentheses the first time the trade name is mentioned.

to virtually all antihistaminics known. These include: a) local anesthetic activity, b) anticholinergic (atropine-like) activity, c) anti-spasmotic activity and d) alteration of the pressure responses to epinephrine. Other actions relating to the electrophysiological properties of the heart are reviewed in another section of this report.

Reports of some of these actions of antazoline as compared to other antihistaminics have been published by Graham (12), Reuse (13) and Dutta (18).

Regarding local anesthetic activity, in certain preparations antazoline was found to be somewhat less potent than Neoantergan and procaine (18). In other tests antazoline was again much less potent than Benadryl and nupercaine but also somewhat less potent than Neoantergan. In general by comparison to other antihistaminics, the local anesthetic activity of antazoline is low.

As an antagonist of the muscarinic effects of acetylcholine (atropine-like action) antazoline also ranks low among antihistaminics. In this respect it is also much less potent than Benadryl (about 30X) and somewhat more potent than Neoantergan (about 2X) (12,13). While most of these tests were made on isolated smooth muscle, the negative inotropic effect of acetylcholine on the isolated atrium is also blocked by Benadryl and antazoline.

As smooth muscle spasmolytic (against $BaCl_2$ concentration) antazoline is less potent than both Neoantergan (about 1/2) and Benadryl (about 1/5) (12).

Antazoline shares with certain other antihistaminics, Antergan, Benadryl, Neoantergan, Pyribenzamine) the property of enhancing the pressure responses of epinephrine. The pharmacodynamic basis of this effect is rather obscure except that it is apparently not related to antihistaminic activity (19).

In addition antazoline as well as Benadryl have been found to have certain effects on the neuromuscular junction and certain ganglionic blocking properties (18). At present, it is difficult to provide a strict pharmacodynamic basis for the above-mentioned as well as a number of other effects that have been ovserved with a variety of antihistaminics. In all probability these actions are related to some underlying basic similarity among all effects which involve membrane phenomena in different cells and tissues. Since antihistaminic, local anesthetic, anticholinergic etc. effects are undoubtedly linked to such membrane mechanisms, it is not surprising to find some overlapping of pharmacological activities.

toxicity of other antihistaminics such as Benadryl and Neoantergan which, in this species, produce death preceded by central nervous system (CNS) excitation and convulsions. However, Graver et al. (14) reported that the toxicity of antazoline in rats is similar to that of other antihistaminics in that death is preceeded by excitement and convulsion.

In dogs, according to Craver et al. (15), intravenous doses up to 8 mg/kg produce no apparent symptoms. Larger doses (8-15 mg/kg) produce apprehension, tremor, restlessness and hyperpnea with excessive salivation and emesis following the larger doses. These effects, including convulsions, are readily counteracted by the administration of CNS depressants such as barbiturates or chloroform. Death is preceeded by convulsions at dose levels exceeding 18 mg/kg. Similar effects were obtained by these workers in the same species with oral doses between 15-30 mg/kg while an oral dose of 10 mg/kg produced no toxic symptoms. In two dogs given 10 mg/kg intravenously, Angelakos and Driscoll (35) confirmed the observations of Craver et al (15).

In man the toxic effects of antazoline are reported as being similar to those of other antihistaminics (11) consisting of nausea, drowsiness, drying of mouth, dizziness and tachycardia which may follow the usual dose level of 50-100 mg orally. Too rapid intravenous injection may cause flushing and vertigo.

The largest doses of antazoline that have been reported to be administered in man are those used in connection with its antiarrhythmic activity (20,21,22). Doses up to 10 mg/kg intravenously were administered by Dreifus et al (21) and by Reynolds et al (22). The latter workers used total doses as high as 1500 mg given intravenously over 105 minutes. The toxic effects in man are similar to those observed in the dog with nausea and vomiting being the chief toxic reactions at the higher dose level. A more detailed account of the effects observed in connection with the use of such high doses in man is given in another section of this report (see page 20). Generally maximal total intravenous doses of up to 10 mg/kg given slowly at a rate of about 10-20 mg/min. seem to be tolerated by man. We were unable to find any reports of death in man associated with the administration of antazoline. The available information and animal studies suggest that the minimal lethal intravenous dose is of the order of 20 mg/kg although this could probably be greatly extended by the use of barbiturates and other measures to counteract the adverse effects of CNS excitation and convulsions.

As with other pharmacological agents idiosyncrasies and/or allergic reactions may occur in susceptible individuals even at minimal dose levels.

IV. ANTI-ARRHYTHMIC ACTIVITY.

A. Experimental Studies

Antazoline had been included in a number of screening tests for selecting antiarrhythmics together with a variety of other antihistaminics, local anesthetics and related compounds. Most of these studies were done in isolated heart muscle preparations and are reviewed in the first part of this section. Systematic studies, using intact animals, were first done in connection with arrhythmias occurring under hypothermia by Angelakos and Hegnauer (5-8). Their results were subsequently confirmed in the same type of arrhythmia by Brown (23). More recently other workers have tested the effect of antazoline in other types of experimental arrhythmias (20). All of the studies made in intact animals are reviewed in the latter parts of this section.

1. Action on isolated heart muscle preparation.

The method of Dawes (24) has been used as a screening test to determine the "antiarrhythmic" or "quinidine-like" activity of a variety of pharmacological agents. The method consists of the determination of the maximum rate of stimulation to which an isolated heart muscle preparation is capable of responding without interruption. This is taken as reflecting the "refractory period" of the preparation. However more specific studies involving strength-interval measurements throughout the cycle indicate that measurements made with Dawes method are affected not only by changes in refractory period but also by changes in excitability as well as by other alterations involving the relationship between cycle length and refractoriness. In general this is not a very specific test, which is perhaps the reason that a large number of compounds which have been shown to have an "antiarrhythmic" activity by this test often do not exhibit any significant activity against experimental or clinical arrhythmias.

Antazoline was tested using Dawes method by Dutta (18), and it was found to be somewhat more potent than quinidine but less potent than Benadryl. This action was interpreted by Dutta (18) and later by Burn (25) as supporting the theory that quinidine-like activity is related to a blockade of the excitatory effects of acetylcholine in the heart. Acetylcholine is known to decrease

the refractory period of atrial muscle in isolated preparations and in the intact dog heart (26,27). However specific pharmacological studies made by Torchiana and Angelakos (27) with the classical antiarrhythmics indicated that blockade of the excitatory effects of acetylcholine on the heart was not related to quinidine-like action.

In a series of preliminary experiments made by Torchiana and Angelakos (28) antazoline was tested on its ability to antagonize the shortening of the refractory period produced by acetylcholine in isolated preparations of the rabbit atrium. Using specific measurements as previously reported (27) no significant activity was found in these specific studies with concentrations of antazoline up to 10^{-4}.

In view of these latter observations, and the well known poor specificity of the Dawes test, it does not seem likely that antazoline owes its antiarrhythmic activity to an anti-acetylcholine action. On the other hand the activity of antazoline in this test suggests a possible direct action on the refractory period or on excitability or a more complicated effect. Further specific studies are needed to clarify this point.

2. Spontaneous hypothermic ventricular fibrillation.

The high incidence of ventricular fibrillation in man and dog has been fully documented (1). In data collected in a large series of dogs in this laboratory (2) the median heart lethal temperature was 20.1°C with 95% confidence limits of 18.9 to 21.3°C. In man the lethal body temperature is apparently near 25°C (1). Virtually all the deaths occurring above 20°C in dog and man are due to ventricular fibrillation.

A variety of accepted or potential antiarrhthmic agents have been tested on their ability to prevent the development of hypothermic ventricular fibrillation (5 thru 8, 29 thru 33).

In the initial screening studies made by Angelakos and Hegnauer (6) against spontaneous ventricular fibrillation none of the five animals treated with 5 mg/kg of antazoline developed ventricular fibrillation, and the mean lethal temperature was reduced significantly from 19.2°C in the controls to 17.3°C in the treated group. This decrease in temperature represented an increased survival of from one to two hours in the iced bath. Among all other compounds screened at that time (and since that publication), only quinidine and chloromethapyrilene (another

In general, considering all the properties commonly encountered among antihistaminics, antazoline is in no way different from other closely related compounds. Quantitatively it generally ranks in the bottom of the list on both antihistaminic activity and other pharmacological effects (local anesthetic, anticholinergic, antispasmotic). Thus its specificity as an antihistaminic is also low. It is like Neoantergan, the most specific antihistaminic known, regarding low activity in non-antihistaminic pharmacological effects, but unlike Neoantergan, its antihistaminic potency is also low.

C. Toxicity

Part of the available information on the acute toxicity of antazoline is summarized in Table I.

Table I. Acute toxicity of antazoline.

SPECIES & Rx		Min. Tox. Dos. mg/kg	LD 50	REFERENCE
Mouse	(i.v.)	20	60	(10)
Mouse	(i.p.)	--	120	(12)
Mouse	(s.cu.)	150	200	(10)
Mouse	(p.o.)	250	400	(10)
Rat	(i.v.)	--	39	(14,15)
Rabbit	(i.v.)	5	30	(10)
Rabbit	(i.v.)	--	16	(14,15)
Rabbit	(s.cu.)	50	20	(10)
Rabbit	(p.o.)	150	>600	(10)
Dog	(i.v.)	18	--	(14,15)
Dog	(i.v.)	8	>30	(10)

The acute intraperitoneal LD 50 in mice of 120 mg/mg listed in the table can be compared with 125 mg/mg for Neoantergan and 100 mg/mg for Benadryl observed by the same workers in parallel tests.

Graham (12) reported that in mice toxic doses of antazoline produce motor ataxia followed by central nervous system depression and eventually death from respiratory failure. This is unlike the

antihistaminic) gave similar results, i.e., no ventricular fibrillation in five animals and a significant reduction in lethal temperature.

On the basis of these screening tests a number of compounds including antazoline, quinidine, and chloromethapyrilene were tested in a range of doses using ten animals per dose. The results for quinidine, antazoline, and chloromethapyrilene, the most active compounds, are reproduced in Table II.

Table II. Incidence of ventricular fibrillation and lethal temperatures following treatment with selected compounds from Angelakos and Hegnauer (6).

Drug	Dose mg/kg	No. of Dogs	Per cent of VF		Lethal Temp°C
			Terminal	Above 19°C	Mean*
Controls	--	20	90	75	20.6
Quinidine	5	10	90	60	19.0
	10	20	45	10	16.9
Chloromethapyrilene	5	10	20	10	16.6
	10	10	10	0	16.1
Antazoline	2	10	90	40	17.3
	5	10	30	20	15.9
	10	10	20	0	14.9

*Median lethal temperatures and 95% confidence limits are also given in the original publication (6).

The superiority of antazoline is quite evident from these results. In particular the reduction of the mean lethal temperature by 5°C from the controls represents a prolongation in survival by several hours.

A number of other observations indicate that in the dog the lower limit of hypothermic temperatures, in the absence of ventricular fibrillation, is of the order of 12 to 15°C. Below this range pacemaker failure and cardiac asystole occurs (2).

Similar results were obtained by Angelakos and Hegnauer (8) in animals cooled to 20 ± 1°C. At this temperature level a large proportion of the control untreated animals terminated in ventricular fibrillation. The results obtained with quinidine and antazoline are shown in Table III.

Table III. Incidence of fibrillation in dogs cooled to 20 ± 1°C for Angelakos and Hegnauer (8).

	Dose mg/kg	No. of Dogs	Per cent of Deaths (VF)
Controls		20	60
Antazoline	10	20	10
	10	20	0
Quinidine	10	20	20

Subsequent rewarming resulted in an overall high mortality in all groups. It was shown that this was associated with the development of acute heart failure in the groups treated with the antiarrhythmic agents (8). However, this could be prevented by the administration of sympathomimetic amines or by prior digitalization (8).

Similar studies on the effect of antazoline in hypothermic ventricular fibrillation in dog and man were made subsequently by Brown and associates (23). Although no details have been published by these authors, they have reported that they have confirmed the findings of Angelakos and Hegnauer.

3. Hypothermic ventricular fibrillation following ventriculotomy.

It has been shown that the incidence of spontaneous ventricular fibrillation can be reduced by controlling blood pH and preventing the development of respiratory acidosis which occurs under

hypothermia (3). However, under these conditions ventricular fibrillation still occurs in a high proportion of animals when right ventriculotomy (or other mechanical or electrical stimulation of the ventricle) is performed at heart temperatures of 25°C (34). The comparative activity of antazoline and quinidine to protect from ventricular fibrillation during right ventriculotomy was studied by Angelakos and Hegnauer (5,7). Some of their results are reproduced in Table IV. Again antazoline was superior to quinidine and all other compounds tested. The table includes observations at a dose level of 20 mg/kg for antazoline and quinidine from data collected in this laboratory which have not been previously reported (35).

Table IV. Incidence of ventricular fibrillation following right ventriculotomy at heart temperature of 26 ± 1°C (10 animals per group). From Angelakos (7).

Drug	Dose (mg/kg)	Per cent ventricular fibrillation
Controls	--	60
Quinidine	5	60
	10	10
	20	10*
Antazoline	5	40
	10	5
	20	0*

*Angelakos and Driscol (35).

4. Other experimental arrhythmias.

Kline et al (20) reported experiments in four dogs in which antazoline (dose not reported) terminated the ventricular tachycardia induced by an injection of sand into the distal portion of the left circumflex artery.

5. Electrophysiological observations.

Although a systematic study was not made, no significant electrocardiographic (ECG) effects were noted when antazoline was injected into hypothermic or normothermic dogs(5 thru 8). A similar lack of ECG effects have been reported by Kline et al (20) in their studies in patients. This included observations on P-R interval, QRS duration, ST segments and T waves. In a subsequent study by the same group (21), they reported a temporary increase in QRS duration after large intravenous doses of antazoline in only two patients and again no change in the Q-T interval.

Watanobe et al (36) reported on the effect of antazoline on the membrane potentials of the isolated perfused rabbit heart. They found that perfusion with 10 mg/l of antazoline reduced the maximum rate of depolarization by more than 50% of control with little or no change in the action or resting potentials. Similar results were obtained with the same concentrations of quinidine and procaine amide. This effect on the rate of depolarization was found to be dependent on the potassium ion concentration of the perfusing fluid; high potassium enhancing the effect while low potassium increased the maximum rate of depolarization toward control levels.

In view of the large concentrations used, corresponding to in vivo intravenous doses of roughly 20 to 100 mg/kg, it is difficult to interpret the significance of these findings. They may be taken to suggest that in large doses antazoline may be expected to produce a slowing in myocardial conduction velocity. This in turn would be expected to produce an increase in QRS duration which is in agreement with some clinical observations made with large doses. Watanobe et al (36) do not mention any effect of even these large doses on the duration of the action potential. This is in agreement with the clinical and experimental findings showing no effect on the Q-T interval of the ECG. This in turn suggests that antazoline has no significant effect on the refractory period.

Direct preliminary studies made by Torchiana and Angelakos (28) revealed no significant effect of antazoline on the refractory period of the isolated rabbit atrium in concentrations up to 0.1 mg/l.

B. Clinical Studies.

As far as can be ascertained from the available literature use of antazoline as an antiarrhythmic in man was first reported in 1952 by McKechnie (37). This investigator reported one case with frequent ventricular ectopic beats which was successfully treated with 200 mg of antazoline orally three times a day. In the same patient, this arrhythmia was also terminated by similar administration of quinidine (300 mg), Benadryl (50 mg) or intravenous procaine amide. The effect of antazoline in this case was not specific and the author concluded that all antihistaminics should be tested further in clinical arrhythmics. McKechnie noted that following antazoline, hyperventilation produced depression of ST segment and flattening of the T waves. This was not observed following treatment with quinidine. Larger doses of antazoline (300 mg t.d.s.) produced headache, nausea, vomiting and diarrhea in this patient.

More recently the effect of antazoline in clinically observed arrhythmias in man have been studied extensively by two groups of investigators and their results have appeared in three reports by Kline et al , Dreifus et al and Reynolds et al (20,21,22).

The clinical observations made in these studies are summarized in Tables V through XIV and are discussed below. Since the etiology and pathophysiology of the arrhythmias observed clinically vary considerably, it is necessary to evaluate the effect of antazoline in each, more or less distinct, pathophysiological entity. Unfortunately, the published data on the underlying disease associated with each arrhythmia are not complete, therefore the discussion must be based primarily on the electrocardiographic diagnosis of the arrhythmia. This is particularly true since in many cases the etiology of the arrhythmia is not known with any degree of certainty. The distribution of the principle types of heart disease in each of the studies is shown in Table V.

Table V. Distribution of patient diagnoses associated with the arrhythmias treated with antazoline.

Reference	(20)	(21)	(22)
Total no. of:			
Patients	40	112	115
Arrhythmias	40	141	137
No. of patients with:			
No heart disease	12	9	25
Arteriosclerotic heart dis.	19	69	45
Rheumatic heart dis.	2	27	10
Other heart dis.	7	7	35
Median patient age (years)	59	?	60

1. Treatment of various arrhythmias.

a. Atrial extrasystoles. As is apparent from Table VI, antazoline is highly effective in suppressing atrial extrasystoles following oral treatment with 100 to 200 mg four times a day. A much higher success rate was reported by Kline, et al. (20) and Dreifus, et al (21) than by Reynolds, et al (22). However, in the latter case a more extensive period of observation was used. It is also possible that different proportions of the underlying disease states were included in each of these three studies. However, in general, antazoline appears quite effective in suppressing atrial extrasystoles.

Table VI. Responses* of atrial extrasystoles in man to treatment with antazoline.

Dose (mg)	No. of Patients	No. Responding	Reference
100 (x3) p.o.	6	6	(20)
100-200 (x4) p.o.	14	14	(21)
Up to 10 mg/kg i.v.	1	1	(21)
100-200 (x4) p.o.	24	12	(22)**
Totals	45	33	

*Response: Decrease in the number of ectopics by 70% or more.
**This study involved a more extensive period of observation.

b. Ventricular extrasystoles. Table VII summarizes the results reported for the treatment of this arrhythmia with antazoline. As in the case of atrial extrasystoles, antazoline appears to have a very definite action in suppressing ventricular extrasystoles. These results confirm the initial case report by McKechnie (37). Again, distinct differences are noted in the results from the various groups of investigations but the overall conclusion appears to be the same.

Table VII. Responses* of ventricular extrasystoles in man to treatment with antazoline.

Dose (mg)	No. of Patients	No. Responding	Reference
100 (x3) p.o.	22	19	(20)
100-200 (x4) p.o.	61	57	(21)
Up to 10 mg/kg i.v.	7	7	(21)
100-200 (x4) p.o.	35	18	(22)**
Totals	125	101	

*Response: Decrease in the number of extrasystoles by more than 70%.
**This study involved a more extensive period of observation.

c. Atrial tachycardia. The observations on the treatment of paroxysmal atrial tachycardia with antazoline are summarized in Table VIII. In many cases treatment with antazoline was successful in terminating this arrhythmia. This was particularly true when treatment was given intravenously during an attack. However, paroxysmal atrial tachycardia with block as seen with digitalis excess was not terminated in two cases treated by Dreifus et al. (21). Instead reversion of the block with 1:1 A-V conduction was observed and treatment was terminated.

Table VIII. Response* of Paroxysmal atrial tachycardia in man to treatment with antazoline.

Dose (mg)	No. of Patients	No. Responding	Reference
50-200 i.v.	3	2	(20)
Up to 10 mg/kg i.v.	13	12	(21)
100-200 (x6) p.o.	9	4	(22)
Totals	25	18	

*Response: Termination of the arrhythmia and conversion to sinus rhythm.

Table X. Response* of atrial fibrillation in man to treatment with antazoline.

Dose (mg)	No. of Patients	No. Responding	Reference
100 (x3) p.o.	3	1	(20)
100-200 (x4) p.o.	14	1	(21)
Up to 10 mg/kg i.v.	4	0	(21)
200 (x4) p.o.	1	0	(22)
100-200 (x6) p.o.	4	1	(22)
100-200 (x6) p.o. and 400 (22 min) i.v.	1	0	(22)
100-200 (x6) p.o. and 1500 (105 min) i.v.	1	0	(22)
Total	28	3	

*Response: Conversion to normal rhythm.

f. Ventricular Tachycardia. Perhaps the most striking and beneficial effect of antazoline was in the treatment of ventricular tachycardia. A high rate of success in terminating this arrhythmia has been observed after intravenous treatment (Table XI). It appears that large doses up to 10 mg/kg or higher, given in a slow infusion are needed. Reynolds, et al (22) used intravenous infusion of 10-20 mg/min. for a total dose of 400-600 mg. and was successful in terminating the tachycardia in most cases.

Table XI. Response* of ventricular tachycardia in man to treatment with antazoline.

Doses (mg)	No. of Patients	No. Responding	Reference
200-800 i.v.	4	2	(20)
Up to 10 mg/kg i.v.	10	6	(21)
400-600 (30 min) i.v.	5	4	(22)
Totals	19	13	

*Response: Termination of the tachycardia and conversion to normal rhythm.

g. Ventricular Fibrillation. The clinical information regarding the effect of antazoline on this arrhythmia is of necessity limited. Reynolds, et al (22) reported that they felt that antazoline was beneficial in two patients in preventing attacks of ventricular fibrillation as well as facilitating electrical defibrillation. Further studies are needed to evaluate the effect of antazoline in this arrhythmia in man.

h. Nodal Rhythms. The effect of antazoline was studied in a variety of nodal rhythms including nodal tachycardia, paroxysmal nodal tachycardia, passive and accelerated nodal rhythm, etc. The number of cases in each category were limited and the results are variable (Table XII). This probably reflects the heterogeneity of the etiological factors involved in this group. Some success was obtained by Dreifus, et al (21) in correcting passive and accelerated nodal rhythms secondary to advanced A-V block due to digitalis excess.

Table XII. Response* of various nodal rhythms in man to treatment with antazoline.

Dose (mg)	No. of Patients	No. Responding	Reference
Up to 10 mg/kg i.v.	8	1	(21)
100-200 (x4) p.o.	6**	4	(21)
100-200 (x6) p.o.	5	1	(22)
Totals	19	6	

*Response: Conversion to normal rhythm.
**Passive and accelerated nodal rhythms.

2. Treatment of Digitalis Toxicity.

All three clinical reports give evidence that antazoline is effective in suppressing some of the arrhythmias associated with digitalis toxicity. Thus, Kline, et al (20) reported a case of ventricular tachycardia due to digitalis toxicity which was treated successfully with 300 mg of antazoline intravenously. The report of Dreifus et al (21) included 17 arrhythmias due to digitalis excess and antazoline was found to abolish ventricular extrasystoles and in some cases also nodal tachycardia. However, as previously mentioned in cases of paroxysmal atrial tachycardia with block, antazoline enhanced A-V conduction. Reynolds, et al (22) reported that antazoline was effective in supressing paroxysmal atrial tachycardia due to digitalis excess in at least one patient.

However, Angelakos et al (38,39,40) have shown in experimental animals that agents which prevent arrhythmias due to digitalis

d. Atrial Flutter. All available reports agree that antazoline has little or no effect in converting atrial flutter into normal sinus rhythm following oral treatment (Table IX). Similarly no response was obtained by Dreifus et al (21) in one patient treated with a large intravenous dose. However, Reynolds et al (22) were successful in converting one patient with thyrotoxicosis after 350 mg of antazoline intravenously. The same workers noticed that antazoline treatment resulted in some slowing of the atrial rate even though conversion did not take place.

Table IX. Response* of atrial flutter in man to treatment with antazoline.

Dose (mg)	No. of Patients	No. Responding	Reference
100 (x3) p.o.	2	0	(20)
100-200 (x4) p.o.	2	0	(21)
Up to 10 mg/kg i.v.	1	0	(21)
100-200 (x6) p.o.	3	0	(22)#
350 i.v.	1	1**	(22)
Totals	9	1	

*Response: Conversion to normal rhythm.
**Patient with thyrotoxicosis.
#All patients showed some slowing of the atrial rate even though conversion did not take place.

e. Atrial Fibrillation. Again the results of the effect of antazoline on clinically observed atrial fibrillation are uniformly negative (Table X). No conversion to normal sinus rhythm was accomplished in most cases even when large doses were administered intravenously. In two of the three cases where conversion was successful, the fibrillation had developed acutely during cardiac catheterization. In general antazoline seems to be of little value in the treatment of atrial flutter or fibrillation as currently observed clinically.

excess do not necessarily protect from the lethal effects of digitalis. Therefore, it remains to be shown whether antazoline is effective in preventing death from digitalis toxicity. Nevertheless, from a clinical point of view, prevention of digitalis arrhythmias is in itself desirable since it would tend to improve the hemodynamic status of the patient.

3. Dosage.

The experimental studies suggested that dosage levels similar to those used for quinidine should be employed.

From the clinical reports it appears that oral treatment with as little as 100 mg. three times a day may be effective. However, in many cases, 100-200 mg. four to six times a day may be necessary and as much as 100-200 mg. every one to two hours have been employed. Nevertheless, in most cases the total dose was limited to less than 800 mg. per day. Intravenously, doses up to 1500 mg. (over 105 minutes) have been given. However, most responses have been obtained with total doses of 400-800 mg. given slowly. Infusions of 10-20 mg./min. to a total dose of up to 10 mg/kg of body weight seem to be appropriate especially in cases of severe ventricular tachycardia where termination of the arrhythmia may be life saving.

Generally the incidence of side effects is increased with the higher doses, and rapid intravenous administration may have other undesirable effects on the cardiovascular dynamics (see below).

4. Side Effects.

As may be anticipated, the incidence of side effects is related to the dose. When small doses (100 mg. three times a day) were used as in the study of Kline, et al (20) the side effects were minimal and were limited to lightheadedness, nausea and drowsiness in about 10% of the patients. In the study of Reynolds, et al (22) where larger doses were used (100-200 mg. two to six times a day) the incidence and severity of side effects was higher. A partial list of the most common or severe side effects as reported by Reynolds, et al (22) is given in Table XIII. It is clear that about 20% of the patients had severe side effects but this included patients receiving very large doses. On the other hand, about one-third of the patients had some minimal or transient side effects. Similar results have been reported by others (20, 21, 37).

Nausea or vomiting, the chief side effect, could be prevented in most patients by giving the drug with the meals or with an antacid preparation. Other serious side effects which were attributed to the drug and required discontinuation of medication were: chills

and fever with eosinophilia, severe diarrhea, neurologic effects such as uncontrollable tremor, and marked scaling dermatitis.

Table XIII. Side effects associated with treatment with antazoline. Abstracted from Reynolds, et al (22).

	No.
Total Patients	108
Total Side Effects	60
Transient or minimal	39
Severe	21*
Nausea/vomiting	37
Drowsiness/fatigue	18
Diarrhea	5
Dizziness/lightheadedness	4

*Includes 5 patients receiving very large doses.

5. Summary of the Clinical Studies.

The overall results from all clinical studies to date have been summarized in Table XIV. It should be re-emphasized that this summary included results from a rather heterogeneous number of cases and a variety of disease states (Table V). Nevertheless, several pertinent conclusions can be drawn. Generally antazoline seems to be effective in atrial and ventricular extrasystoles and in ventricular tachycardia and perhaps also in some cases of atrial tachycardia and nodal rhythm. By contrast antazoline is generally ineffective in atrial flutter and atrial fibrillation. The value of this compound in ventricular fibrillation in man appears promising, but remains to be established.

Table XIV. Summary of the response* of cardial arrhythmias in man to treatment with antazoline.

Arrhythmia	No. of Patients	No. Responding	% Responding
Atrial			
Extrasystoles	45	33	73
Parox. Tachycardia	25	18	72
Flutter	9	1	11
Fibrillation	28	3	11
Ventricular			
Extrasystoles	125	101	81
Tachycardia	19	13	68
Nodal			
Var. rhythms	19	6	32
Total	270		

*Response: Termination of arrhythmia and/or conversion to normal rhythm (see also Tables VI to XII.)

Unfortunately in most cases the available clinical studies do not provide information regarding the relative value or potency of antazoline as compared to other antiarrhythmics such as quinidine and procaine amide. Only a few observations have been reported in this respect which do not permit any valid comparisons. Considering the spectrum of activity of the three drugs it would appear that antazoline may be particularly useful in cases of ventricular tachycardia. Similarly antazoline may be effective in arrhythmias associated with A-V block where quinidine is contra-indicated. In this connection Dreifus et al (21) reported two patients with third degree A-V block due to myocardial infarction in which treatment with antazoline resulted in normal A-V conduction. Furthermore, antazoline appears to be an effective non-toxic drug for the treatment of premature atrial or ventricular contractions and possibly as preventive in paroxysmal tachycardias (22).

C. Mode of Action

There are a variety of hypotheses regarding the mode of action of antiarrhythmic compounds. It has been suggested that prolongation of the refractory period may serve as the basis for antiarrhythmic properties. Antazoline has been shown to decrease the maximum rate at which isolated atria can be driven which is generally considered as an indication of increased refractory period (18,25); more recent observations, using direct measurements of the refractory period (28) confirmed the indirect measurements. However antazoline shares the property of increasing the refractory period with a variety of other antihistaminics (18, 24,25). On the basis of these observations it does not appear likely that the antiarrhythmic activity of antazoline can be attributed simply to its effect in increasing the refractory period. In fact the hypothermic heart is highly susceptible to arrhythmias and fibrillation even though there is a striking increase in refractory period which is generally more pronounced than the concurrently observed increase in conduction velocity (41,42,43).

Another mode of action suggested is in connection with an anti-acetylcholine effect of antazoline on cardiac muscle (18,25).

In preliminary experiments made by Angelakos and Torchiana (28), antazoline was studied for its ability to counteract the excitatory effects of acetylcholine in cardiac muscle. These studies were similar to those performed with atropine and the classical antiarrhythmic agents in isolated atrial preparations and in the intact animal (27). Again in this respect, antazoline did not

exhibit any significant or specific activity.

In general no single or combination of the known effects of antazoline is sufficiently distinctive to account for the anti-arrhythmic activity of this compound as compared to other anti-histaminics and related substances. Since many of the latter compounds tested have no antiarrhythmic activity under hypothermia, it seems that the basis of the antiarrhythmic activity of antazoline remains essentially unknown. Further studies are warranted in this direction since knowledge on the mode of action of known antiarrhythmics would provide the necessary background for the systematic development of more effective compounds.

V. OTHER CARDIOVASCULAR EFFECTS.

Antazoline, when injected intravenously, produces a transient decrease in blood pressure. Both systolic and diastolic levels decrease and in general the available evidence indicates that this hypotension is due to both cardiac depression and peripheral vasodilation.

Previous studies made in this laboratory indicated that a state akin to acute heart failure developed in a large proportion of hypothermic animals treated with antazoline during subsequent rewarming (8). It was found that this condition could be treated successfully with the use of positive inotropic agents such as the sympathomimetic amines or by prior digitalization (8).

More recent studies (44,45) indicate that antazoline, when injected intravenously in dogs in large doses, produces a decrease in myocardial contractility as measured by the Walton-Brodie strain gauge arch. At the same time the peak rate of rise of intra-ventricular pressure (dP/dt) is reduced. In this respect antazoline acts similarly to all other antiarrhythmic agents that have been studied. All such agents, including quinidine and procaine amide, have been found to produce a transient depression of myocardial contractility (45,46,47).

Generally it appears that the effect of antazoline on myocardial contractility is the major limitation regarding its use in large intravenous doses. However this effect appears to be of relatively short duration (at least in the normothermic animal and man) and can be minimized through the use of slow intravenous infusions.

No studies appear to have been made on the action of antazoline on the coronary circulation or other regional circulatory dynamics. Similarly it is not known whether the hypotensive effect of antazoline is at all related to a possible interference with the normal sympathetic tone or is associated with a direct action on the blood vessels. Antazoline, like other antihistaminics and related compounds, in large doses, has non-specific antispasmogenic activity on smooth muscle.

VI. CONCLUSIONS.

From the information available in the literature antazoline appears to be an effective antiarrhythmic compound in both animals and man. Its antiarrhythmic activity first discovered in connection with its action in protecting from hypothermic ventricular fibrillation seems to extend to a variety of arrhythmias observed in man in association with heart disease. In hypothermic ventricular fibrillation and in some of the clinically observed disorders, the antiarrhythmic activity of antazoline is often superior to that of quinidine. However antazoline when used in high doses has distinct side effects similar to those observed with large doses of other antihistaminic compounds.

The antiarrhythmic activity of antazoline does not appear to be related to its antihistaminic, anticholinergic, local anesthetic or other known pharmacologic properties. Although antazoline prolongs the refractory period of heart muscle its antiarrhythmic activity, at least under hypothermia, does not appear to be dependent on this property. In general the electrophysiological basis of the antiarrhythmic effect of antazoline is at present unknown.

Antazoline in large doses produces transient hypotension and depression of myocardial contractility. These side effects it shares with other antiarrhythmic agents such as quinidine and procaine amide.

In spite of these limitations the available evidence, both experimental and clinical, indicate that antazoline is useful antiarrhythmic agent in a number of specific arrhythmias including those associated with hypothermia.

A D D E N D U M

Note: Since the preparation of this report the reviewer became aware of another publication* of the use of antazoline in the treatment of clinical arrhythmias. Although the results given in that publication are essentially the same as those reviewed in the body of the report, nevertheless, for the sake of completeness, a summary of the results included in the publication is presented below.

In a report published in 1963* Leon-Sotomayer presented results on 24 patients treated for cardiac arrhythmias with antazoline. The drug was used intravenously in doses up to 400 mg and/or by mouth in doses of 200 mg every 6 hours.

Auricular fibrillation. Out of 12 patients treated, six (50%) responded to antazoline by conversion to sinus rhythm. Two more (17%) responded to antazoline only after digitalization while four (33%) did not respond.

Atrial flutter. No response was obtained in 4 patients treated with antazoline.

Digitalis toxicity. Five patients showing arrhythmias associated with digitalis overdose were all reverted to normal sinus rhythm after antazoline.

Miscellaneous arrhythmias. In single cases with a) complete A-V block, b) arrhythmias due to myocardial infarction and c) Wolff-Parkinson-White syndrome, antazoline did not produce satisfactory results. However one case of paroxysmal atrial tachycardia was treated successfully with antazoline.

Side effects. The side effects observed by this author were similar to those reported by others and incorporated in the body of the report. They included (number of patients in parentheses), dryness of mouth (6), nausea and vomiting (4), defecation (3) and finger tremor (4). In addition 2 patients showed hypotension on rapid intravenous injection, one patient showed temporary hallucinations, and another grand mal convulsions.

The author concludes that most of the common side effects of the drug are due to its anticholinergic properties.

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*Leon-Sotomayer, L.: A clinical evaluation of the antiarrhythmic properties of antazoline. Am. J. Cardiol. 11:646-653, 1963.

Mechanism. On the basis of ECG observations consisting of alterations in the Ta wave and QRS complex, the author suggests that the action of the compound is on the atrial refractory period. His conclusion that the drug has little or no effect on the electrophysiological properties of the ventricle is not supported by previous and subsequent experimental and clinical observations.

Conclusion: The author suggests that antazoline be used for the treatment of atrial arrhythmias and especially those associated with intraventricular conduction defects (such as partial A-V block and bundle branch block) where quinidine is contraindicated. However he does not recommend the use of the compound in arrhythmias associated with longstanding third degree A-V block.

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13. ABSTRACT

The chemistry and general pharmacology of antazoline and experimental studies employing it are reviewed to determine the antiarrhythmic activity and the protective effect of antazoline against hypothermic ventricular fibrillation. In hypothermic ventricular fibrillation and in clinically observed heart disorders, the antiarrhythmic activity of antazoline was often superior to other pharmacological agents, including quinidine. The incidence of side effects, notably nausea or vomiting, was found to be related to the dosage. Since the basis of the antiarrhythmic activity of antazoline is essentially unknown, further studies in this direction are warranted to provide for systematic development of more effective compounds.

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There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

14. KEY WORDS: Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context. The assignment of links, rules, and weights is optional.