Reports on Therapy

A Clinical Trial of Antazoline in the Treatment of Arrhythmias*

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THE quinidine-like action of the antihistamines was first observed by Dews and Graham[1] and confirmed by Dutta.[2] Dutta[3] then observed that antazoline (Antistine,® Ciba), an antihistamine introduced by Meier and Bucher,[4] appeared more active than quinidine. Clinical interest was stimulated by the Angelakos and Hegnauer[5,6] studies in dogs showing that antazoline, as well as other antihistamines, and quinidine afforded high protection against ventricular fibrillation in hypothermia. The over-all survival was limited by the development of acute heart failure in many treated animals that escaped ventricular fibrillation, but this could be overcome by inotropic agents. Kline and Dreifus and their associates[7,8] observed that in dogs intravenous antazoline caused a transient reduction in cardiac output and a rise in peripheral resistance, with the blood pressure and heart rate remaining constant. In clinical trials among 112 patients with 141 disturbances of rhythm they found antazoline to be an effective, well tolerated antiarrhythmic agent which was useful in the therapy of ectopic beats of atrial, nodal or ventricular origin. It was ineffective in the conversion of atrial flutter and atrial fibrillation.

Thus, animal studies and preliminary clinical trials provided evidence that antazoline has antiarrhythmic actions in addition to its known antihistamine effects. Because the preliminary studies were encouraging, it was felt that further trials in many different kinds of disturbances of cardiac rhythm were indicated.

MATERIAL AND METHODS

The present series consisted of 115 patients with 137 cardiac arrhythmias selected from the medical and surgical wards of the University of Michigan Hospital, the Heart Station and the Ann Arbor Veterans Hospital. With the exception of patients with atrial fibrillation and atrial flutter, some of whom were not included in the study, the selection represented no known bias toward any one group. No other conditions were so handled, and the number of patients with other arrhythmias approximately represented their incidence during the period of the study. To avoid eliminating those patients who might not respond or who might have early side effects, no patients were dropped from the study because of poor follow-up or inadequate data.

More than one half of the patients were over 59 years of age. There was no associated heart disease in 25 patients; 45 had coronary artery disease; 10 had rheumatic heart disease; and the remainder had miscellaneous kinds of heart disease. There were 13 deaths, and 9 postmortem examinations were made. None of the deaths could be attributed directly to antazoline, but all occurred in patients in the terminal phase of their disease.

All patients were evaluated by one or more of the authors during periods of hospitalization and in the follow-up visits to the Heart Station. There the arrhythmia was investigated by reviewing the patient's report card with him to determine the dates, duration and frequency of paroxysmal arrhythmias and by taking a three-minute count of the number of premature beats and/or monitoring their frequency with a recording cardiotachometer for from 15 minutes to 24 hours.

Where circumstances permitted, a control period and/or trial on another antiarrhythmic agent for an equal or greater period was used in lieu of placebo

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TABLE I
Effectiveness of Antazoline in Conversion of Cardiac Arrhythmias

Disturbance of Rhythm	No. of Cases	Effect— Good	None
Paroxysmal atrial tachycardia	2	1	1
Atrial flutter	4	1	3
Atrial fibrillation	7	1	6
Ventricular tachycardia	5	4	1
Ventricular fibrillation (see text)	2	2	0

control. A control period on a placebo, using the single-blind technic, was satisfactorily accomplished for long periods of time in only 5 patients. Recurrence of paroxysms of supraventricular arrhythmia which were unpleasant to the patient and paroxysmal ventricular tachycardia or other threats to the patient's life, plus inadvertent knowledge or suspicion by the patient that he was receiving a placebo, were the main reasons for failure of the planned placebo control period. In many other instances such a placebo control period could not be obtained or was not needed, as, for example, in the conversion of cardiac arrhythmias.

Comparison of antazoline with other antiarrhythmic drugs was accomplished by monitoring 13 patients with the recording cardiotachometer for 24 hours on no antiarrhythmic drug and for 24 hours each on at least two other drugs, such as quinidine sulfate, procaine amide, Alderlin® (Ayerst), atropine, digitalis and reserpine, and by counting the frequency of premature beats in the 24 hour period. This method is more precise than other methods of counting premature beats, but because it became available late in the study, and few patients were studied in this way, the results are not tabulated separately.

RESULTS

Abolition of cardiac arrhythmias, prevention of paroxysms of rapid heart action and the prevention of premature beats are separate aspects of this study and will be considered separately.

ABOLITION OF ABNORMAL RHYTHM

Attempts were made to terminate abnormal cardiac rhythm in 19 patients, and the results are listed in Table I.

Atrial Flutter and Fibrillation: Conversion of atrial flutter or atrial fibrillation was attempted 11 times in 10 patients, both conditions occurring in 1 patient at different times. There was one successful conversion of each. Of the 4 patients in whom unsuccessful attempts were made to terminate atrial flutter, 3 received only oral medication with multiple dosage schedules of 100 or 200 mg. every one or two hours for six doses. The one success occurred in a 70 year old woman with thyrotoxicosis given 350 mg. intravenously, with prompt conversion. The patient died one week later, possibly due to an overdose of chloral hydrate and other causes. All patients treated had slowing of the atrial rate, whether or not conversion took place.

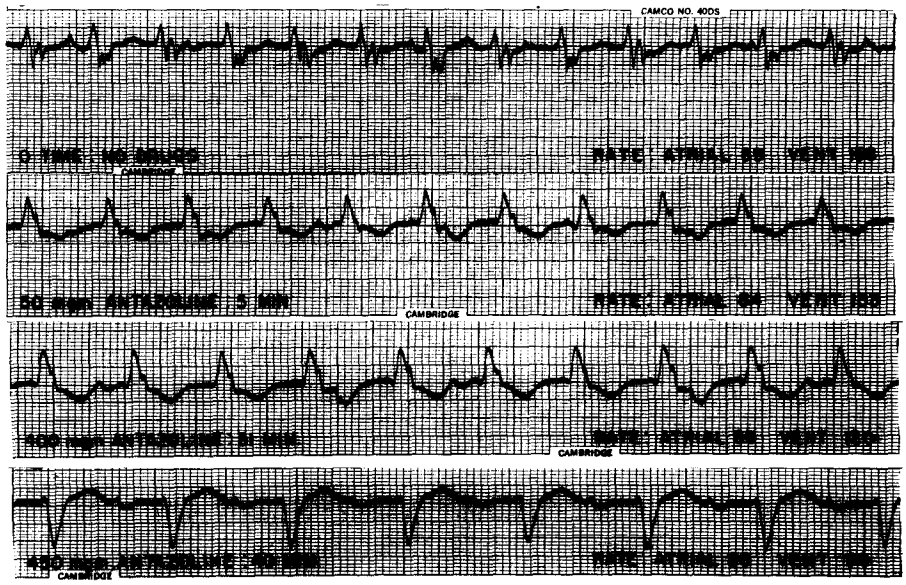

FIG. 1. Sequential electrocardiographic tracings of lead V_2 showing the termination of ventricular tachycardia with 450 mg. of antazoline intravenously.

TABLE II
Effectiveness of Antazoline in the Prevention of Paroxysmal Cardiac Arrhythmias*

Disturbance of Rhythm	No. Patients	Effect				Insufficient Data
		Good	Moderate	Slight	None	
Premature beats						
Atrial	28	9	3	6	6	4
Ventricular	41	12	6	5	12	6
Undiagnosed	4	...	1	1	...	2
Nodal	3	1	...	...	2	...
Paroxysmal arrhythmias						
Atrial tachycardia	10	2	2	2	3	1
Nodal tachycardia	2	...	...	1	...	1
Undiagnosed tachycardia†	9	1	1	1	2	4
Atrial flutter	6	...	...	1	3	2
Atrial fibrillation	8	...	...	2	4	2
Ventricular tachycardia	6	...	1	1	2	2
Total	117	25	14	20	34	24
Per cent of total	100	21.4	12.0	17.1	29.0	20.5

* In the prevention of paroxysmal arrhythmias or premature beats the following limits apply to the evaluation: *Effective:* Rhythm studied ceases altogether or with less than 5 per cent residual breakthrough. *Moderate:* Suppression of rhythm studied reaches 70 per cent, with 30 per cent or less residual breakthrough in number of attacks or numbers of premature beats. *Slight:* Data are not always conclusive, but the evidence shows some suppression of the rhythm studied.

† No ECG obtained during attack.

In 7 patients in whom attempts to abolish atrial fibrillation were made, only 6 received an adequate dosage. The seventh patient, treated early in the study, received only 200 mg. four times a day. Of the remaining 6, 1 received 400 mg. of antazoline intravenously in 22 minutes, and in addition to the oral schedules listed here, 1 received 1,500 mg. intravenously in 1 hour and 55 minutes, with only mild symptoms and without converting his rhythm. The one success was achieved in a 43 year old man who developed atrial fibrillation during cardiac catheterization, which persisted for five days prior to the attempt at conversion, during which time he was fully digitalized. The effective dose was 100 mg. each hour for four doses. Normal sinus rhythm persisted after the conversion. The oral schedules used in the unsuccessful attempts were 100 or 200 mg. every one or two hours. In 1 case the schedule was 300 mg. every two hours for six doses.

Ventricular Tachycardia: By far the best results were obtained in the abolition of ventricular arrhythmias. Out of 5 patients with ventricular tachycardia, 4 were converted to normal sinus rhythm, by using 400 to 600 mg. of antazoline diluted and given intravenously over a 30 minute period. The one failure was in an unconscious patient with fresh myocardial infarction and ventricular tachycardia who subsequently died. Prior to death the QRS complexes became wide and were of sine wave configuration, resembling potassium intoxication. Figure 1 illustrates the sequence of a successful conversion of proved ventricular tachycardia.

Ventricular Fibrillation: Two patients experienced cardiac arrest due to ventricular fibrillation, and it is felt that antazoline was effective in preventing a recurrence of this rhythm after electrical countershock conversion of the ventricular fibrillation. In one of these patients ventricular tachycardia developed after ventricular fibrillation was converted with electric countershock. The ventricular tachycardia was then treated by giving 200 mg. of procaine amide intravenously. Ventricular fibrillation recurred, and after a considerable period of cardiac massage, 100 mg. of antazoline was given intravenously, and the rhythm returned to a normal sinus mechanism within 10 minutes. Normal rhythm was maintained for two weeks, at the end of which the patient died of pulmonary complications.

The second patient had a fresh posterolateral myocardial infarction with ventricular fibrillation, which recurred after each of two attempts of electrical defibrillation. Antazoline, 600 mg., was given intravenously, and the third electrical conversion was successful in that normal sinus rhythm persisted. It is obvious that antazoline

was useful only in conjunction with alternating current defibrillation, but both of these encouraging outcomes would seem to justify further study of antazoline in ventricular fibrillation.

PREVENTION OF PAROXYSMAL ARRHYTHMIAS

Evaluation of the ability of antazoline or any antiarrhythmic agent to prevent attacks of rapid heart action is most difficult, for the groups studied were not homogeneous in any sense except for the rhythm disturbance itself. The frequency of attacks, presence of heart disease, age group and presence of associated anxiety are all factors that cannot be eliminated by group study of the type described here. Thus, each patient had to serve as his own control. The rhythm disturbances, with few exceptions, were so intermittent that they could not be documented, and so reliance had to be placed on a report card system. Table II lists the results of the use of antazoline in this group of patients.

Prevention of Premature Beats: Antazoline in an oral dose of 100 or 200 mg. four times a day was effective or moderately effective in 12 of 24 patients with proved frequent atrial premature beats in which study was adequate and in 18 of 35 patients with ventricular premature beats.

Figure 2 illustrates how evaluation was made in a patient with many premature beats. The patient, a 58 year old white man, had a two year history of rapid heart action every two months. He was admitted to the hospital following such an attack, during which he lost consciousness while driving and crashed into a tree. The electrocardiogram revealed ventricular premature beats, and the 24 hour continuously monitored heart rate revealed an average of 126 ventricular premature beats for each 16 minute period during the 24 hours. This figure compares with the 24 hour average of 37 every 16 minutes during antazoline therapy. This represented a 71 per cent reduction, and therefore the drug was considered moderately effective, with a 29 per cent residual breakthrough. Although moderately effective, it was not as

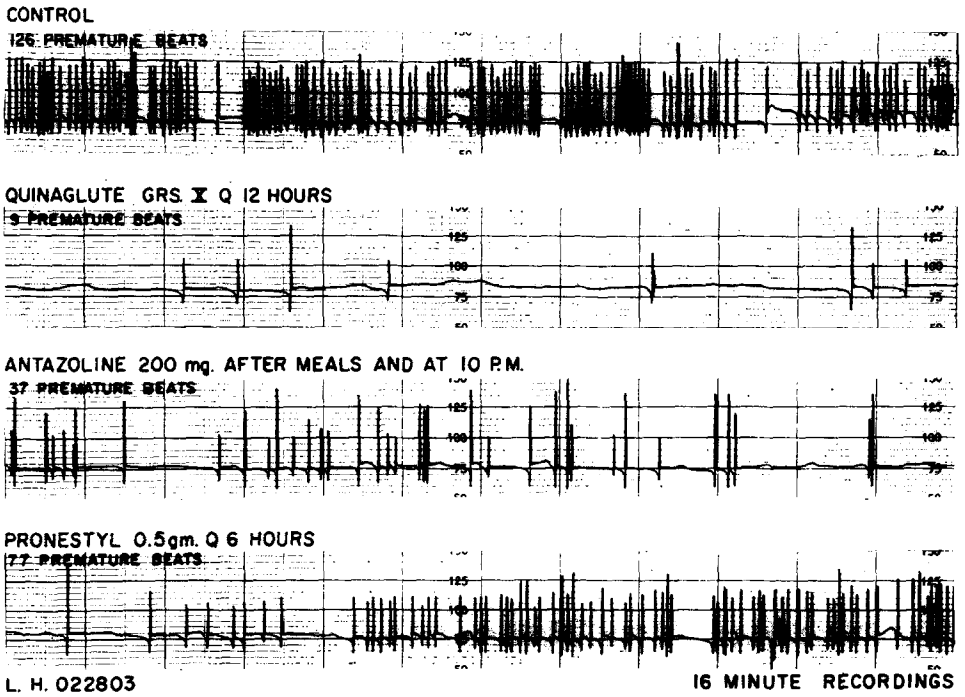

FIG. 2. Digital cardiotachometer recordings made during four successive 24 hour periods of drug therapy. The records are read from right to left and are measurements made from the R-R interval of the electrocardiogram: Heart rate = 60/R-R(sec.). Thus, each premature beat appears as a vertical line, the top of which indicates the shorter R-R interval (faster rate) followed by a compensatory pause (slower rate). These 16 minute samples were selected from 24 hour recordings, so that the number of premature beats shown corresponds with the 24 hour average for the particular drug studied. The lower strip shows the onset of action of procaine amide one hour after the drug was taken. The suppressive effect shown to the left lasted one hour. The other drugs studied showed more uniform action.

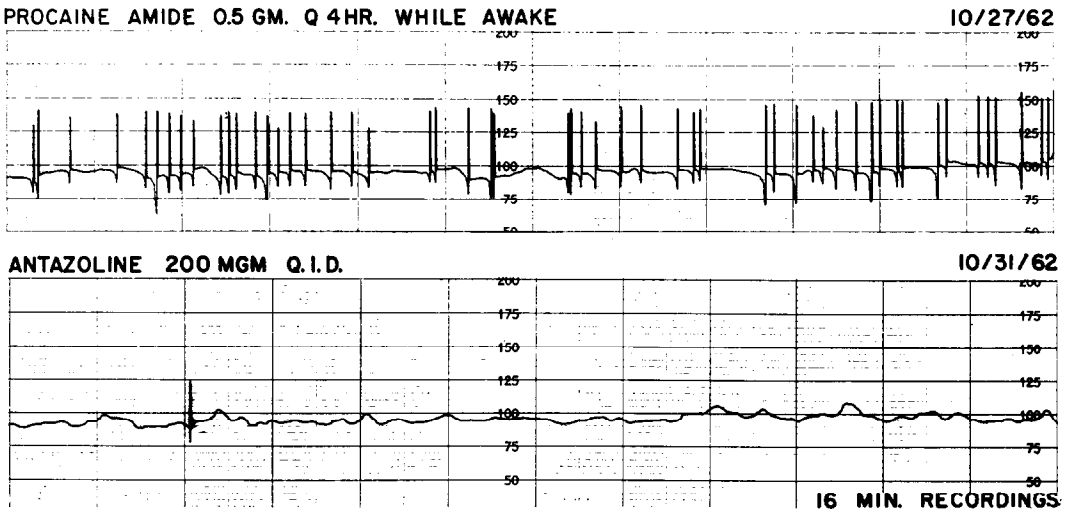

FIG. 3. Paroxysmal ventricular tachycardia and ventricular premature beats in a 60 year old man. These two selections from 24 hour recordings show the superiority of antazoline compared with procaine amide in suppressing ventricular premature beats.

effective as quinidine in the prevention of premature beats in this patient. Since the follow-up period was only one month, it was not felt proper to evaluate the effectiveness in the undiagnosed rapid heart action, although the patient was free of attacks during this period. Figure 2 was prepared by selecting samples from the 24-hour recordings that corresponded with the number of premature beats as shown by the 24 hour average in this patient.

The next 5 patients illustrate clinical situations where therapy of premature beats appeared justified to prevent the occurrence of a more serious arrhythmia.

Figure 3 is a cardiotachometer record taken on a 60 year old man with paroxysmal ventricular tachycardia proved by electrocardiograms. In addition, he had frequent ventricular premature beats during the period of ineffective treatment with procaine amide. Antazoline was effective in suppressing both disturbances of rhythm.

Figure 4 is a record from a 49 year old woman who had fresh myocardial infarction on the day the tracings were taken. It shows two strips of electrocardiograms taken several hours apart and is representative of the clinical situation as observed over a two month period. Bigeminy, seen in the first tracing, was abolished by antazoline but recurred two months later when the drug was discontinued and ceased again when the drug was restarted. It has not recurred in a further six month period of antazoline therapy.

Figures 5 to 7 illustrate the value of continuously monitoring the heart rate of patients to evaluate both the dose (Fig. 5) and choice of drug (Fig. 6 and 7) needed to suppress premature beats in patients with coronary artery disease.

Prevention of Paroxysmal Tachycardia: There

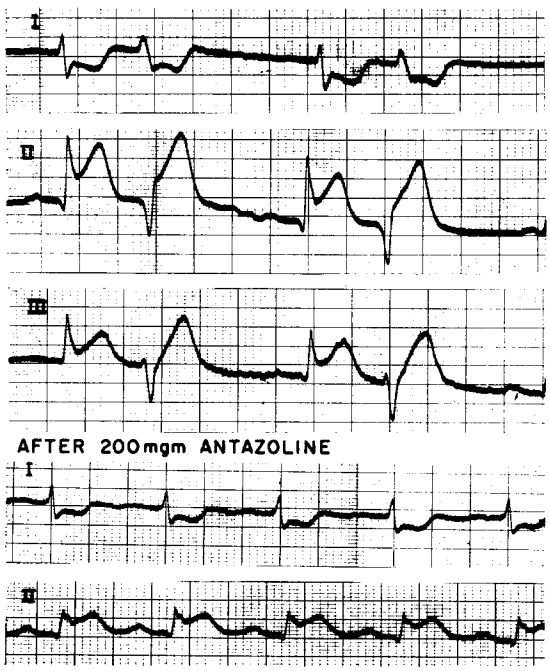

FIG. 4. Bigeminal rhythm following fresh posterior myocardial infarction was effectively controlled with antazoline.

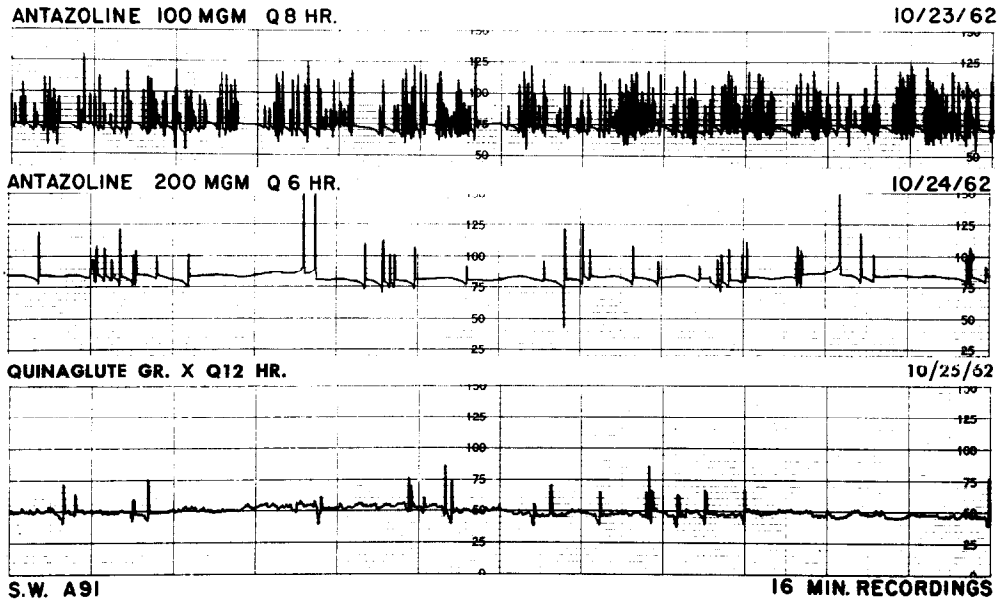

FIG. 5. Acute myocardial infarction and frequent atrial premature beats in 39 year old woman. Representative recordings from three 24 hour periods of drug therapy show the frequency of premature beats for two dose ranges of antazoline compared with a long-acting quinidine preparation.

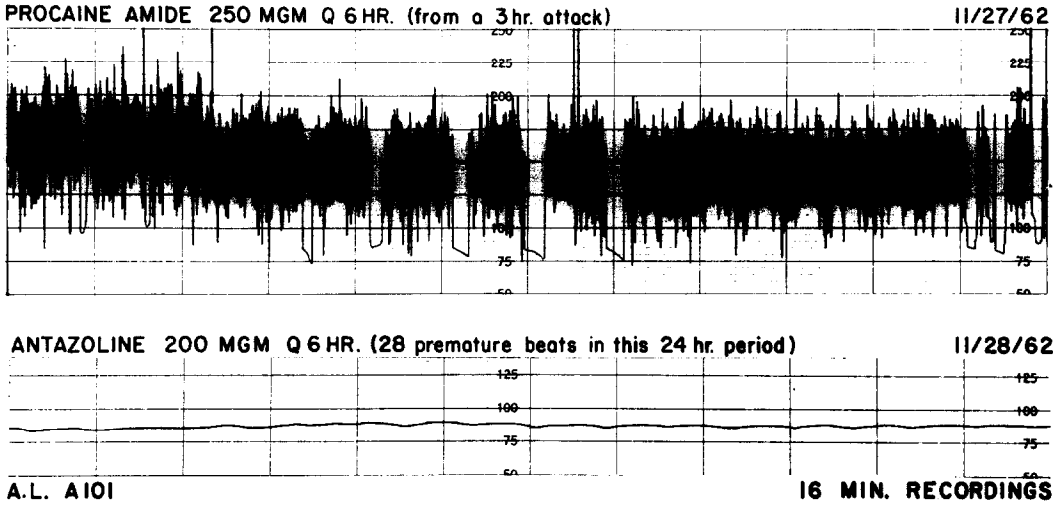

FIG. 6. Fresh myocardial infarction and atrial bigeminy in a 65 year old man. Antazoline in the dose shown was effective in suppressing the atrial premature beats; procaine amide was ineffective.

were 10 patients with *paroxysmal atrial tachycardia*. Of 2 in this group who had recurrent atrial tachycardia due to digitalis intoxication, antazoline was effective in 1; the second patient was given other drugs such as potassium chloride making it quite impossible to evaluate any effects of antazoline other than the side reactions. The remaining 8 patients were followed up from 4 to 12 months (average, 7.7 months) to determine the frequency of recurrent attacks of atrial tachycardia, and antazoline was found at least moderately effective in 3.

Antazoline was used to prevent *paroxysmal atrial flutter* in 6 patients on follow-up for an average of 8.9 months and in *paroxysmal atrial fibrillation* in 8 patients followed for an average of 7.9 months. One of these patients was followed for 21.5 months and had 18 attacks of atrial fibrillation in $5^1/_2$ months under no therapy, 5 attacks in 3 months of placebo therapy, and

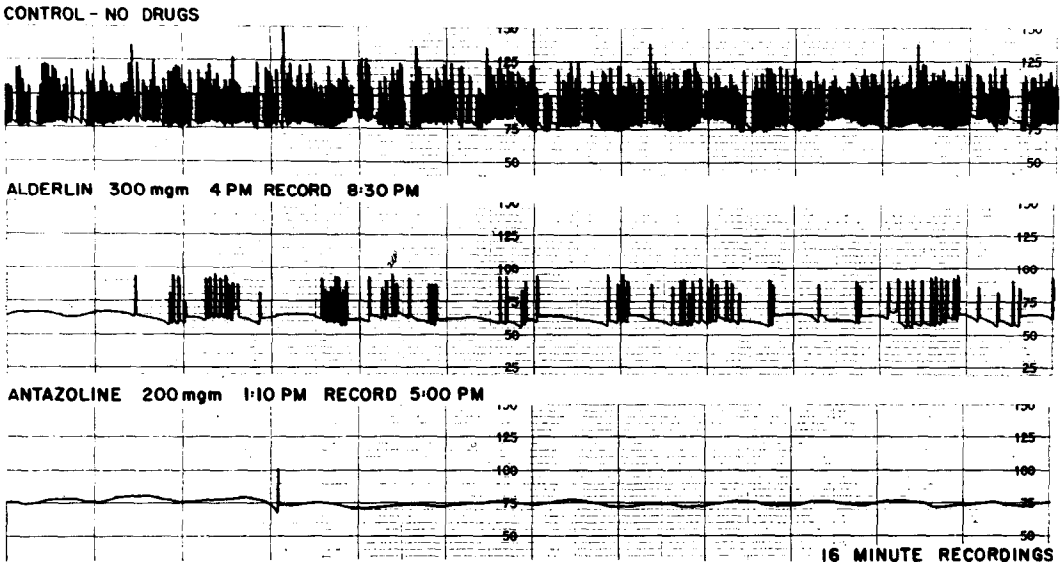

FIG. 7. Tracings from a 69 year old woman with angina pectoris and almost constant atrial premature beats during the 24 hour control period (upper trace). Alderlin, a beta adrenergic blocking agent, was slightly effective (middle trace), but antazoline was classed as the most effective. The dose, time of administration and the time the record was taken are shown.

14 attacks in 13 months while receiving antazoline in 100 and 200 mg. doses four times a day. This was felt to be a significant reduction in number of attacks but was interpreted as only slightly effective. The effects of the drug in 1 of the patients with paroxysmal atrial fibrillation could not be evaluated because he had received only the placebo before being lost to follow-up. The results in another patient could not be evaluated because the paroxysmal atrial fibrillation simply disappeared and failed to return after the drug was stopped. In 4 patients on follow-up for 3, 7, 14 and 17 months respectively, the drug was ineffective. One of these patients had an adequate quinidine trial, which was also ineffective.

Six patients with *paroxysmal ventricular tachycardia* were studied. In 1 of the patients in whom the drug was considered ineffective, ventricular premature beats could be suppressed by antazoline. In the 1 case in which the drug was moderately effective there was no known heart disease, but the patient experienced repeated attacks of syncope due to ventricular tachycardia over a 27 month period of observation. These attacks could not be prevented by quinidine sulfate, quinidine gluconate in a long-acting preparation or by procaine amide. Seven attacks of ventricular tachycardia were observed in one month. Antazoline in a dose of 100 mg. 4 times a day was also ineffective, but when the dose was increased to 200 mg. four times a day, the number of attacks was reduced to less than one a month (8 total in 10 months of observation on antazoline).

SIDE EFFECTS AND TOXIC REACTIONS

Table III lists the frequency of side actions in 108 of the patients. Side effects could not

TABLE III
Side Effects and Toxic Reactions in 108 Patients

	No. of Patients	% of Total
Total patients having side effects	60	55.6
Transient or minimal	39	36.1
Severe	21*	19.4*
Side effects		
Anorexia only	5	4.6
Nausea and/or vomiting	37	34.3
Drowsiness and/or fatigue	18	16.7
Diarrhea	5	4.6
Epigastric distress	7	6.5
Dizziness and lightheadedness	4	3.7
Weakness	6	5.6
Other†	15	13.9

* Includes 5 patients receiving large doses for rhythm conversion.

† Headache, chills, fever, muscle spasm, clouded sensorium, disorientation, confusion, full-feeling in head, tremor, scaling dermatitis of hands and scalp, abdominal cramps, eosinophilia, aberration of QRS complex, flushed sensation and hiccoughs.

be evaluated in the remaining 7 patients because of poor reporting. *Nausea* or *vomiting*, or both, constituted the chief side effect, and this could be prevented in most patients by taking the drug with meals or with an antacid preparation. The second most frequent side effect was drowsiness, but it was not severe enough to necessitate stopping the drug. Few severe side reactions were encountered, but these are worth reporting. They were as follows:

Chills and Fever: A 65 year old physician was given 100 mg. of antazoline four times a day as prophylaxis against frequent attacks of rapid heart action which, as judged by the history, resembled atrial tachycardia. The number of attacks was reduced, but the patient had headache, chilliness, nausea and a temperature of 103.5° F. The symptoms subsided completely when antazoline was stopped. One month later the drug was resumed, and after the patient took the second dose he again had nausea, chilliness and a temperature of 103.5° F. The white blood cell count was 10,000, with 16 per cent eosinophils. The symptoms subsided when the drug was stopped. One additional tablet was taken three months later, and the patient again had nausea, diarrhea and fever (101.5° F). There was no history of asthma or hay fever in this patient.

Diarrhea occurred in only 5 per cent of the patients, but when it occurred it was often severe enough to necessitate stopping the drug. One case will illustrate this point:

A 66 year old woman had many ventricular premature beats occurring in runs, which constituted her "attacks." These were slightly reduced by actual count during antazoline therapy, and the drug was considered slightly effective after a 6 month study period. Mild nausea and diarrhea were noted at the onset of therapy, but these symptoms were not severe enough to stop therapy. By the fifth month the patient was having five to six watery stools daily. When antazoline was stopped, the symptoms disappeared, only to recur when antazoline was given again.

Neurologic Side Effects: Five patients had symptoms referable to the central nervous system. These symptoms were described as the "shakes" and consisted of uncontrollable tremor that occurred in 1 patient with a dose of 200 mg. four times a day and disappeared when the dose was reduced to 100 mg. four times a day. One patient experienced nausea and severe paresthesias of all four limbs following 350 mg. of antazoline given intravenously in a 15 minute injection for successful conversion of ventricular tachycardia to normal sinus rhythm. Another patient, a 61 year old man with many ventricular premature beats, became profoundly depressed and had a clouded sensorium on 100 mg. of antazoline four times a day. These symptoms disappeared, and the ventricular premature beats were controlled intermittently (result coded as ineffective) on a dose of 50 mg. four times a day. A fourth patient, given 100 mg. of antazoline four times a day for frequent ventricular premature beats, experienced lightheadedness and muscle spasm of the legs. A fifth patient, a 53 year old woman, had many atrial and ventricular premature beats occurring in runs following repair of an atrial septal defect. She became disoriented when given 200 mg. of antazoline every six hours. This symptom cleared after antazoline was stopped for two days.

Skin Eruption: A single patient had a marked scaling dermatitis of his hands and scalp after receiving 200 mg. of antazoline three times a day for four months. These lesions cleared after the drug was stopped for two weeks.

Summary

Antazoline is a comparatively safe and effective antiarrhythmic drug in many situations, for both the conversion and prevention of arrhythmias. It appeared to be most effective in the abolition of ventricular tachycardia, possibly helpful in 2 cases of cardiac arrest due to ventricular fibrillation and beneficial in the prevention of atrial and ventricular premature beats. It was useful and deserves further trial in the prevention of paroxysmal ventricular tachycardia. It was almost ineffective in the conversion and prophylaxis of atrial flutter and atrial fibrillation but appeared to be of value in the prevention of paroxysmal atrial tachycardia.

There was a high incidence of mild side effects, mostly of the gastrointestinal type, some of which were prevented by taking the drug with meals or with an antacid preparation. No irreversible or serious side actions were encountered, but diarrhea, central nervous system symptoms and chills and fever necessitated stopping the drug in a small percentage of patients.

Acknowledgment

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