BETA-ADRENERGIC RECEPTOR BLOCKADE IN CARDIAC ARRHYTHMIAS

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Black and Stephenson (1962) reported that beta-adrenergic receptor blockade with pronethalol produced marked bradycardia in animals. They suggested that this substance might prove helpful in the management of atrial fibrillation and in ventricular and atrial tachycardias by reducing the cardio-sympathomimetic responses to emotion and exercise. The purpose of this paper is to report our experiences with this drug in a variety of cardiac arrhythmias and to discuss its possible therapeutic applications.

Atrial Fibrillation

Clinical Material and Methods.—In hospital practice it is uncommon to see patients with atrial fibrillation who have not already been digitalized. In fact, only four such patients were encountered during the period of this study. We therefore decided to select for trial patients with atrial fibrillation whose resting ventricular rates were not satisfactorily controlled by adequate digitalization or who stated that they experienced rapid palpitation on effort. The use of digitalized patients, moreover, enabled studies during exercise, before and after pronethalol, to be carried out which would scarcely have been practical in patients with uncontrolled ventricular rates. Exercise was carried out using a simple stepping test at a work level of 300 kg. metres a minute. The exercise was continued for five minutes (or less if the patient was unable to complete five minutes). The heart rate was continuously recorded electrocardiographically, both at rest and throughout the periods of exercise and recovery, using a bipolar lead with a suction electrode in each axilla. In five patients the ventilatory cost of exercise was also recorded by the method of Hugh-Jones (1952).

Results

Undigitalized Patients.—The four patients with atrial fibrillation who had not received digitalis were given pronethalol orally. Two had rheumatic heart disease and two ischaemic heart disease. Before the drug was given their mean resting ventricular rate was 136 (range 120 to 156/min.). The dose of pronethalol was progressively increased over the course of a week from 50 mg. t.d.s. until the resting ventricular rate had fallen to between 75 and 85. Three of the patients required 300 mg. t.d.s. and the remaining patient 200 mg. t.d.s.

Digitalized Patients.—In 10 digitalized patients with atrial fibrillation and rheumatic heart disease the response of the ventricular rate to exercise was studied before and one and a half hours after a single oral dose of 300 mg. of pronethalol. The resting rate was recorded at 15-minute intervals after the drug. In six cases slowing had occurred after 15 minutes and in eight it was maximal after one hour. The mean values for the resting rates and for the rates during the last minute of exercise, before and after the drug, are shown in Table I. In five of these patients the ventilatory cost of exercise was recorded both before and after the drug, but showed no significant change.

TABLE I.—*Heart Rate Before and After Pronethalol*

	Before Pronethalol		After Pronethalol	
	Rest	Exercise	Rest	Exercise
Mean	90	155	69	107
Range	(74–128)	(130–190)	(50–90)	(90–134)

Action of Pronethalol After Atropine.—Three digitalized patients with atrial fibrillation were given 50 mg. of pronethalol intravenously in a 0.5% solution at a rate of 10 mg./min. The heart rate was continuously recorded electrocardiographically. Slowing of the ventricular rate occurred in all three, reaching a maximum after 15 minutes. At least 24 hours later each patient was given 1.2 mg. of atropine intravenously, followed 10 minutes later by a further 50 mg. of pronethalol intravenously. Table II shows the individual changes in ventricular rate which occurred. As might have been anticipated, atropine did not block the action of pronethalol, although the final heart rate following both drugs was substantially higher than the resting rate.

TABLE II.—*Heart Rate in Three Digitalized Patients with Atrial Fibrillation*

Case No.	Pronethalol		Atropine		After Pronethalol
	Before	After	Before	After	
1	73	60	67	102	76
2	72	64	68	112	86
3	69	67	68	100	86

Clinical Application.—Although in most cases of atrial fibrillation digitalis satisfactorily controls the ventricular rate at rest, it is well known that it may fail to prevent an excessive rise in rate in response to exercise. It seemed reasonable to suppose that the combination of pronethalol and digitalis might prove useful in the management of atrial fibrillation, more particularly in patients with mitral or tricuspid stenosis. In the presence of significant mitral stenosis, if the cardiac output remains constant, the mean left atrial pressure will vary inversely as the square of the diastolic filling time per minute. Since acceleration of the heart is accomplished by a substantially greater shortening of diastole than systole, patients with mitral stenosis are particularly intolerant of a rapid ventricular rate. The same considerations apply to tricuspid stenosis.

Twenty patients with atrial fibrillation and mitral stenosis and one with tricuspid stenosis were given maintenance doses of pronethalol by mouth, at the same time continuing their digitalis. Fourteen had previously had mitral valvotomies but had restenosed. Sixteen of the patients had average resting ventricular rates of 90 or more despite full digitalization. In order to minimize side-effects, the dose of pronethalol was slowly increased to an average dose of 200 mg. t.d.s.

Thirteen of the 21 patients claimed substantial symptomatic improvement when the heart rate was slowed by the drug, usually by at least one clinical grade. In five there was radiological evidence of a reduction in pulmonary venous hypertension. Four of the remaining eight patients were unchanged and four became worse.

Fig. 1 shows the average resting heart rate of each patient on digitalis alone and after the addition of pronethalol. It is of interest that 12 of the 13 patients who were improved had initial average resting heart rates of 90 or more, whereas six of the eight who were unchanged or

became worse had initial average resting rates of 90 or less. Two of the four patients who became worse had rapid heart rates and both were in right heart failure. When the heart rate slowed with pronethalol their heart failure became worse. The remaining two with normal initial rates both developed right heart failure with oedema and both had a brisk diuresis when the drug was withdrawn. (We have also given pronethalol to six other patients in severe heart failure with rapid heart rate. Only one of these improved when the rate was slowed; the other five all became worse.)

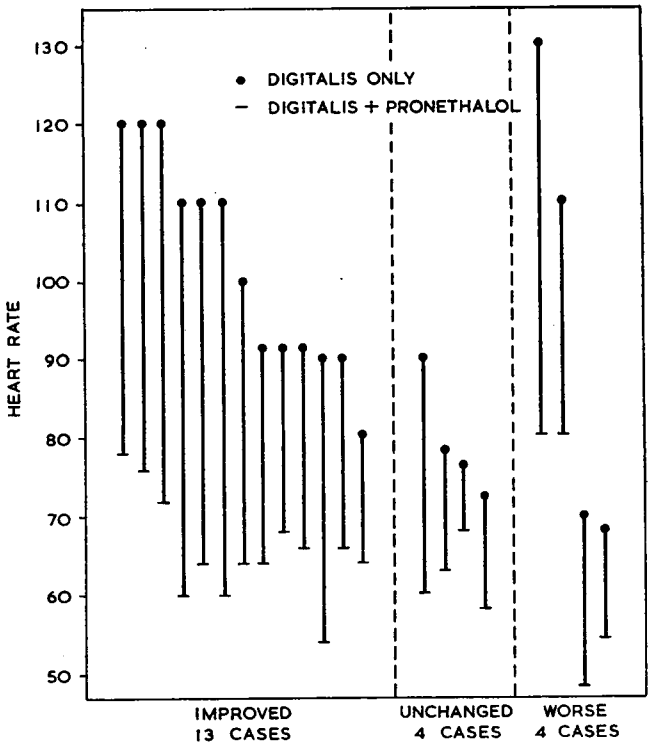

FIG. 1.—Diagram to show the average resting ventricular rates on digitalis alone and after the addition of pronethalol.

Eight of these 21 patients have now been on the drug continuously for nine or more months, so far without evidence of tolerance developing.

Atrial Flutter

Three cases of atrial flutter were given pronethalol in doses of 200 or 300 mg. thrice daily for approximately a week. All three had 2:1 A.V. block. Two of the patients showed slight initial slowing of the atrial rate—in one from 300 to 290 and in the other from 280 to 260/min. In both cases after several days on maintenance dosage the atrial rate returned to its previous value. No change in the degree of A.V. block occurred, and it seems unlikely that the drug will have any useful action in this arrhythmia.

Paroxysmal Tachycardia

Seven patients with intractable paroxysmal tachycardia whose attacks had followed a clearly defined and predictable pattern over at least several months were selected for trial on oral pronethalol. With one possible exception all seven had organic heart disease. In one case the ectopic focus was believed to be ventricular, in four it was known to be atrial, and in the remaining two it was nodal.

Although all seven patients showed initial improvement either by temporary cessation of attacks or by a reduction in their frequency or duration, in only two was the improvement maintained after eight weeks' treatment.

Other Arrhythmias

We have studied the action of pronethalol in a variety of other arrhythmias by giving the drug intravenously under continuous electrocardiographic control. This method has the advantage of allowing the evolution of any changes in rhythm to be studied. Moreover, the use of the intravenous route substantially reduces the likelihood of any changes observed being fortuitous, for the action of the drug is apparent by the time the injection has been completed. The dose varied between 50 and 100 mg., given as a 0.5% solution at a rate of 10 mg./min. A dose of 100 mg. was commonly followed 15 minutes later by vomiting, and latterly we have avoided giving more than 75 mg. A total of 19 patients were studied in this way. In 12 the arrhythmias were unrelated to digitalis medication. The remaining seven had digitalis intoxication.

Arrhythmias Not Due to Digitalis

Extrasystoles

There were three patients with frequent ventricular extrasystoles, two with atrial, and one with both atrial and ventricular. In all six patients the extrasystoles were very frequent, often occurring in pairs and never separated by more than three successive sinus beats. In one of the patients with ventricular extrasystoles and in the patient with both atrial and ventricular extrasystoles no change in the frequency or coupling-time of the extrasystoles occurred after pronethalol. In the remaining four patients the extrasystoles were abolished by the time the injection was completed. A study of the records revealed that the incidence of the extrasystoles first diminished, and as it did so there was a progressive increase in the coupling-time of the ectopic to the initiating sinus beat. For example, in one case with atrial extrasystoles the coupling-time before the drug was given was varying between 0.46 and 0.51 second. Towards the end of the injection the coupling-time of the last four ectopics had lengthened to from 0.68 to 0.74 second.

Atrial and Ventricular Tachycardia

In one patient with atrial tachycardia there was slight slowing of the atrial rate from 180 to 150/min. but the attack was not terminated. There were four episodes of ventricular tachycardia in three patients. In one, a male with a recent anteroseptal infarct, sinus rhythm was restored. Three weeks later, however, he had a second attack. On this occasion there was only slight slowing of the ventricular rate from 150 to 136. In a second patient with ischaemic heart disease there was again only slight slowing of the ectopic tachycardia.

The third patient, also with ischaemic heart disease, had ventricular tachycardia with A.V. dissociation. The sinus cycle averaged 0.55 second (rate 109/min.). The ectopic rhythm was occasionally interrupted by single sinus beats. The individual runs of tachycardia varied in duration from 15 to 75 seconds, with a slightly variable cycle length averaging 0.36 second (rate 167/min.). Each run terminated with a sinus P wave; approximately half of these P waves were followed by a normal QRS, but with a prolonged P–R interval, while the other half were blocked and were followed by a second P wave which was normally conducted with a normal P–R interval of 0.17 second. Clearly, therefore, concealed retrograde conduction (Langendorf, 1948) of the ectopic impulse was occurring and the transient interruptions of the ectopic rhythm took place when the

sinus excitation wave happened to reach the A.V. junction outside its refractory phase, resulting in discharge of the ventricular focus and an "interference beat." After 50 mg. of pronethalol intravenously (Fig. 2) there is a striking reduction in the number of ectopics in each paroxysm to

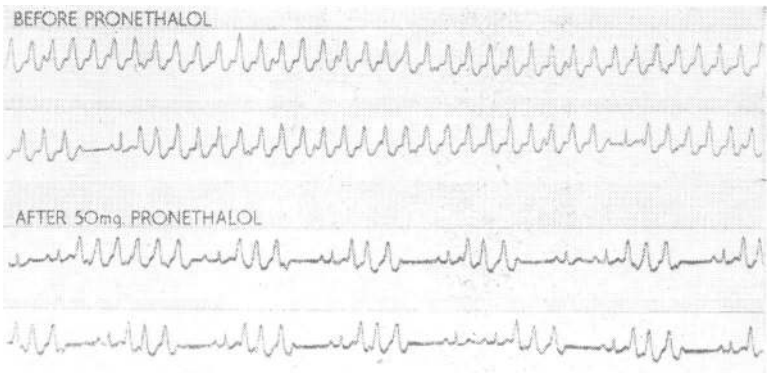

FIG. 2.—Ventricular tachycardia. The upper two rows are a continuous recording of lead II before pronethalol. The lower two rows are a continuous recording of the same lead after 50 mg. of pronethalol intravenously.

three or two, and very often two sinus beats occur in succession. The sinus cycle has lengthened to 0.73 to 0.75 second and the P–R interval is prolonged to 0.22 second. While most paroxysms still terminate with a P wave, all these are now blocked. There is, however, no change in the cycle length of the ectopic focus nor in the coupling-time of the first ectopic beat of a paroxysm to the preceding sinus beat.

Repetitive Paroxysmal Tachycardias

There were two examples—one atrial and one ventricular. In both there was a reduction in the number of ectopics in each paroxysm with an overall reduction in heart rate, but in neither case were the ectopic beats abolished.

Arrhythmias Due to Digitalis Intoxication

A somewhat unexpected finding was that in each of seven patients with digitalis intoxication the toxic rhythm was immediately suppressed by the drug. In one patient with P.A.T. with block, sinus rhythm was restored by the time the injection was completed (Fig. 3). In a second supraventricular tachycardia, sinus rhythm was restored after 25 mg. of the drug had been given. The remaining five patients all had frequent multiform extrasystoles, often occurring in runs, and in each case the ectopic beats had disappeared by the time the injection was completed.

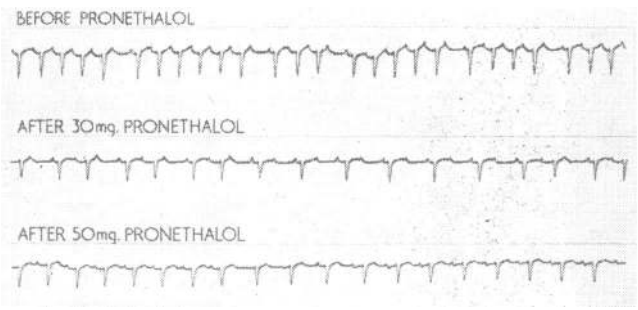

FIG. 3.—P.A.T. with block. All three rows are extracts from lead V 1. In the upper row, before pronethalol, the atrial rate is 180 and there are irregular Wenckebach periods. In the middle row, after 30 mg. of pronethalol, the atrial rate has fallen to 150 and there is 2:1 A.V. block. The lowest row, after 50 mg. of pronethalol, shows restoration of sinus rhythm.

Fig. 4 illustrates the action of intravenous pronethalol in a patient with a digitalis-induced ventricular arrhythmia. Each beat of the dominant rhythm was followed by from one to five ventricular extrasystoles. The individual extrasystoles showed considerable variations in contour, but their coupling-time, both to the initiating beat of the dominant rhythm and to each other, was constant, which is a characteristic feature of digitalis intoxication. After 70 mg. of pronethalol had been given intravenously the extrasystoles had disappeared.

Type II A.V. Block

In contrast to type I partial A.V. block, acceleration of the atrial rate in the less common type II variety increases the degree of block (Mobitz, 1924, 1928; Gilchrist, 1958). Thus abrupt slowing of the ventricular rate may occur in response to exercise or emotion. It seemed that beta-adrenergic blockade might prove useful in the management of this type of block. One case of partial type II A.V. block was encountered during this study.

A man aged 64 had aortic valve disease. His main complaint was of attacks of vertigo and faintness occurring on exertion and also at rest. When first seen as an out-patient he had 2:1 A.V. block with a ventricular rate of 42/min. It was noted that gentle stimulation of the right carotid sinus immediately increased the ventricular rate to 70, a paradoxical effect first reported as characteristic of type II block by Wenckebach and Winterbergh (1927). An electrocardiogram confirmed that carotid sinus stimulation restored 1:1 A.V. conduction by slowing the atrial rate. When admitted for further study he was found to have normal A.V. conduction when resting quietly in bed, with an atrial rate of around 70. Light exercise was performed with continuous monitoring of the electrocardiogram, by getting him to raise his legs alternately from the bed in time to a metronome. In three preliminary trials it required 37, 33, and 36 leg-raisings respectively to induce 2:1 A.V. block, which occurred on each occasion when the atrial cycle length had shortened to 0.72 second. After 50 mg. of pronethalol intravenously it required 165 leg-raisings to produce 2:1 block, which occurred at the same critical atrial cycle length of 0.72 second. Detailed measurement of the electrocardiogram revealed that after pronethalol his improved performance was due to delay in the increase of the atrial rate on exercise. There was no evidence of any change in the relative or absolute refractory periods of the A.V. junction.

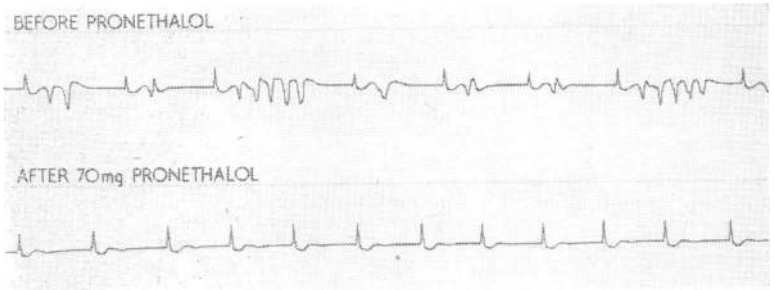

FIG. 4.—Digitalis-induced ventricular arrhythmia before and after 70 mg. of pronethalol intravenously.

Discussion

The observations we have described are clearly at present too limited to justify more than a tentative assessment of

the possible therapeutic value of pronethalol in cardiac arrhythmias. In atrial fibrillation it slows the ventricular rate at least as effectively as digitalis, and when the two drugs are given together their actions summate. The combination, moreover, is much more effective in preventing an excessive rise in ventricular rate on exertion than is digitalis alone. It would seem that the combination of digitalis and pronethalol may be of value in the presence of obstruction of the atrio-ventricular valve and atrial fibrillation, although our limited experience suggests that improvement is likely to be confined to patients whose ventricular rates are not adequately controlled by digitalis alone.

Our experience with paroxysmal tachycardia was not very encouraging, but the cases selected for trial were all intractable and all had proved resistant to quinidine. One would anticipate it might prove particularly useful in those cases where the arrhythmia is precipitated by emotion or exertion—the "tachycardie paroxystique à centre excitable" of Gallivardin.

The suppression of some forms of extrasystoles by pronethalol warrants further study. The observation that as the extrasystoles diminish in frequency their coupling-time to the initiating beat progressively lengthens is of theoretical interest, for it is difficult to reconcile with the re-entry theory of extrasystoles. As pointed out by Scherf and Schott (1959), with a slower ventricular rate due to a reduction in the number of ectopic beats a shortening, not a lengthening, of the coupling-time would be expected.

Pronethalol has the property that it almost always slows the rate of discharge both of the sinus node and of ectopic pacemakers, irrespective of whether these are nodal, atrial, or ventricular. In ectopic tachycardias this effect is occasionally sufficient to restore sinus rhythm, but much more extensive trials will be necessary to assess its value as an anti-arrhythmic drug.

Dornhorst and Robinson (1962) found in healthy subjects that the rise in heart rate on exercise was substantially reduced by pronethalol. It seems likely that this action could be useful in the management of type II partial heart-block, particularly that variety of case recently described by Fowler (1962) whose symptoms are mainly related to exertion. In the one case encountered in this study the action of pronethalol was certainly impressive.

Pronethalol and Digitalis Intoxication.—The immediate suppression of digitalis-induced arrhythmias by promethalol might clearly have considerable therapeutic value; alternatively, it might well prove very dangerous if the action is only to mask the presence of digitalis intoxication. The experimental work of Méndez, Erlij, and Cetrángolo (1962) suggests that pronethalol protects the myocardium against toxic doses of digitalis. These authors investigated the action of digitalis on dogs and cats which had been subjected to surgical or pharmacological sympathetic blockade, and they concluded that the characteristic cardiac phenomenon of digitalis toxicity depends on the presence of circulatory catecholamines, as sympathetic blockade abolishes these actions. It will clearly be important to establish whether a judicious combination of the two drugs may enable digitalis to be continued with benefit in cases where otherwise it would have to be withdrawn.

Pronethalol and Heart Failure.—The aggravation or precipitation of heart failure by pronethalol is disturbing. There are probably at least two factors involved. First, beta-adrenergic blockade will remove the catecholamine drive from the myocardium, which may weaken its force of contraction. Second, slowing the ventricular rate will necessitate an increase in stroke volume if the same cardiac output is to be maintained. If the ventricle involved is unable to reduce its residual volume its end diastolic volume must increase and may reach the "wrong" side of the Starling curve. We certainly feel that the drug should be given with great caution in the presence of established or incipient heart failure.

Summary

The effect of a beta-receptor adrenergic blocking agent, pronethalol, has been studied in patients with atrial fibrillation and other cardiac arrhythmias.

In atrial fibrillation pronethalol effectively controls the ventricular rate, and when combined with digitalis the action of the two drugs summate. When the two drugs are given together they prevent the excessive rise in ventricular rate on exercise which often occurs with digitalis alone. This action appears to be of therapeutic value in some patients with mitral or tricuspid stenosis.

The drug seems to have little effect in atrial flutter or paroxysmal tachycardia, but will abolish some forms of atrial and ventricular extrasystoles.

In seven patients with digitalis-induced arrhythmias the toxic rhythm was immediately suppressed by the drug.

Pronethalol should be given with great care to patients with incipient or established heart failure.

We are indebted to I.C.I. Pharmaceuticals Ltd. for generous supplies of pronethalol.

ADDENDUM.—Since the manuscript of this paper was completed further evidence of the protective effect of pronethalol against digitalis arrhythmias has been provided by the work of Vaughan Williams (1963).

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"A practical way of implementing this is for each clinic to take personal responsibility for interviewing parents and giving explanation and advice concerning the death of their child. . . . There is no doubt about the benefits to the parents in the ways of the relief of anxiety and guilt, the changing of attitudes and help in future decision, especially with regard to family planning. Equally, there is no doubt of the benefit to both the institution and the profession. The public confidence in both the hospital and the profession grows, and doctors, students, and nurses acquire a greater insight into their patients. I doubt if we can afford not to interview parents. It can be salutary to learn from parents that they have, in retrospect, regarded our carefully planned treatment as too enthusiastic. I wonder if survival time is a sound basis on which to judge the success of treatment in a malignant condition such as leukaemia? Do parents really thank us for saving the life of their mentally retarded child by carrying out a tracheostomy for respiratory obstruction? Should we always operate for neonatal intestinal obstruction in the mongol baby? The only way we can learn what parents think about treatment of this type of illness is by discussing it with them at a time when they can consider it more objectively. There is no doubt that their attitude will help influence our future decisions." (Dr. Howard Williams, Royal Children's Hospital, Melbourne. *Med. J. Aust.*, October 19.)