Acute and Chronic Effects of an Adrenergic Beta-Receptor Blocking Agent (Propranolol) in Treatment of Cardiac Arrhythmias

By Myron H. Luria, M.D., Edward I. Adelson, M.D., and Albert J. Miller, M.D.

The introduction of the adrenergic beta-receptor blocking agent, pronethalol, and the more recent availability of its analogue propranolol have served as a new impetus in the pharmacological study of the cardiovascular system. Clinical use of these compounds has been explored in the treatment of hypertension, angina pectoris, prolonged systemic hypotension, hypertrophic subaortic stenosis, and pheochromocytoma.

A fundamental effect of the beta-receptor blocking agents is their ability to slow the heart rate, and for this reason Black and Stephenson suggested their use in certain cardiac arrhythmias. Stock and Dale found that pronethalol slowed the ventricular rate in patients with atrial fibrillation. This effect was particularly noticeable in the digitalized patient.

Although pronethalol (Nethalide; Alderlin) proved to be carcinogenic in mice, its successor, propranolol (Inderal), has not been. Recent studies have demonstrated the latter to be effective in decreasing the frequency of the ventricular response in patients with atrial fibrillation, atrial flutter, and ectopic atrial tachycardia when it was given intravenously. The present report further confirms the ability of propranolol to slow the ventricular rate in digitalized patients with supraventricular arrhythmias. Our experience with the chronic oral administration of propranolol in several different clinical settings is also described.

Methods

Twenty-nine patients ranging in age from 10 to 81 years were studied (table 1). Five to 15 mg of propranolol made up in a 20 mg per 100 ml solution was infused intravenously at a rate of 1 mg per minute in 11 patients. One patient received propranolol intravenously on two separate occasions and subsequently also once by mouth. The drug was given orally for periods of 2 days to 16 months to a total of 21 patients, beginning with a dosage of 10 mg q.i.d. (table 1). When stabilized, the dose of propranolol ranged from 2.5 mg to 40 mg q.i.d. with most patients receiving 20 mg.

The effect of propranolol on the heart rate after exercise was studied in seven patients who were receiving digitalis. During a control period of 3 days, the dosage of digitalis was stabilized and a standard two-step electrocardiographic exercise test was performed daily. Thereafter, treatment with digitalis was continued and propranolol was administered by mouth four times daily. The latter was increased in increments of 10 mg per dose daily until it was concluded that an adequate drug effect, that is, optimal slowing of the heart rate without the undesired effects described below had been obtained. Heart rates were determined during the last 2 days of the control period and during the 2 days of maximum propranolol therapy from repeated electrocardiograms obtained at rest and immediately after exercise. This method was also followed, exclusive of exercise, in more seriously ill patients.

A complete blood count, urinalysis, and determinations of blood urea nitrogen, serum transaminase, and alkaline phosphatase were obtained during the control period, after the maximum dose of propranolol had been established, and at

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Work supported by Grants HE-06375 and HTS-5252 from the National Heart Institute, U. S. Public Health Service.

*Cordially supplied by Dr. A. Sahagian-Edwards of Ayerst Laboratories, New York, New York.
frequent intervals thereafter in each patient receiving the drug chronically. Other laboratory determinations were made as appeared clinically indicated.

Observations

Atrial Fibrillation

The ventricular rate was slowed in all patients with atrial fibrillation when propranolol was given intravenously or orally. The ventricular response at rest was slowed in nine of the 10 patients with chronic atrial fibrillation and the increase in ventricular rate was less after exercise than before propranolol was given in all seven patients exercised (table 2). Seven of these patients were treated with propranolol because of failure to control their ventricular rates at rest or on exercise with large doses of digitalis. In two patients with atrial fibrillation propranolol was also used to slow the ventricular rate before successful conversion to sinus rhythm with quinidine sulfate.

When propranolol was given to patients J.M. and M.A. (table 2), the maximum ventricular rate during two attacks of paroxysmal atrial fibrillation was slowed compared to two previous “control” episodes. In another patient not listed in table 2, bouts of atrial fibrillation were repeatedly induced by exercise. Previous therapy with digitalis and quinidine sulfate had failed to prevent the attacks. However, after the administration of propranolol these paroxysms could no longer be provoked.

The drug was used for 30 days or longer in five patients with chronic atrial fibrillation and in three individuals with paroxysmal atrial

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Intravenous</th>
<th>Oral</th>
<th>&lt; 3 Days</th>
<th>&lt; 30 Days</th>
<th>&gt; 30 Days</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Ectopic atrial tachycardia</td>
<td>4</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Repetitive” atrial tachycardia</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>A-V junctional tachycardia</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Supraventricular tachycardia*</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>11</td>
<td>31</td>
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</tbody>
</table>

*Origin undetermined.

Table 2

Effect of Oral Propranolol on Ventricular Rate in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Heart disease</th>
<th>Digitalis Rest</th>
<th>Digitalis Exercise</th>
<th>Digitalis + propranolol Rest</th>
<th>Digitalis + propranolol Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.B.</td>
<td>M</td>
<td>61</td>
<td>Atherosclerosis</td>
<td>125</td>
<td>145</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>E.R.</td>
<td>M</td>
<td>62</td>
<td>Atherosclerosis</td>
<td>120</td>
<td>120</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>H.R.</td>
<td>M</td>
<td>81</td>
<td>Atherosclerosis</td>
<td>120</td>
<td>120</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>S.V.</td>
<td>F</td>
<td>42</td>
<td>Rheumatic</td>
<td>120</td>
<td>150</td>
<td>110</td>
<td>120</td>
</tr>
<tr>
<td>O.A.</td>
<td>F</td>
<td>29</td>
<td>Rheumatic</td>
<td>82</td>
<td>185</td>
<td>85</td>
<td>110</td>
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<tr>
<td>K.P.</td>
<td>F</td>
<td>37</td>
<td>Rheumatic</td>
<td>110</td>
<td>158</td>
<td>68</td>
<td>130</td>
</tr>
<tr>
<td>R.M.</td>
<td>F</td>
<td>72</td>
<td>Rheumatic</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>S.G.</td>
<td>M</td>
<td>23</td>
<td>Rheumatic</td>
<td>75</td>
<td>120</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>F.K.</td>
<td>F</td>
<td>53</td>
<td>Rheumatic</td>
<td>85</td>
<td>110</td>
<td>55</td>
<td>80</td>
</tr>
<tr>
<td>R.S.</td>
<td>M</td>
<td>60</td>
<td>Rheumatic</td>
<td>57</td>
<td>110</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>M.A.</td>
<td>F</td>
<td>48</td>
<td>Hypertension</td>
<td>140</td>
<td>140</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>J.M.</td>
<td>F</td>
<td>54</td>
<td>Atherosclerosis</td>
<td>150</td>
<td>150</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXIV, November 1966
fibrillation. It was well tolerated by all the patients except S.V. and K.P. These two patients developed congestive heart failure manifested by orthopnea, hepatomegaly, and pedal edema. One patient, R.M., who before therapy was found to have reticulocytosis, developed more extensive manifestations of a hemolytic process. However, this patient was concomitantly receiving numerous other types of medication. No other abnormal laboratory tests which could be related to the use of propranolol were encountered.

Other Ectopic Supraventricular Tachycardias

In a patient with supraventricular tachycardia of undetermined origin, 7.5 mg of propranolol given intravenously did not produce ventricular slowing. Hypotension which developed in this patient was promptly alleviated, without a change in heart rate, by a slow intravenous infusion of isoproterenol. In a 10-year-old child with repetitive atrial tachycardia who was given propranolol orally (20 mg q.i.d.) the pauses between runs of beats were lengthened to greater than 3 seconds (fig. 1). Hypotension also developed gradually, and treatment with the drug was stopped. An elderly lady with paroxysmal atrial flutter was given six 10-mg oral doses of propranolol in addition to substantial amounts of digitalis glycoside. Sinus rhythm with sino-atrial block occurred and continued for 1 week after administration of both drugs was stopped. Another patient had paroxysmal A-V junctional tachycardia which could be readily induced by exercise, smoking, and amyl nitrite. This response was abolished when 40 mg q.i.d. of propranolol was given without altering her usual maintenance dose of digitalis (fig. 2). On subsequent continued propranolol therapy she suffered only one episode of rapid heart action in 3 months, as opposed to its previous daily occurrence.

Ventricular Tachycardia

A 46-year-old housewife had persistent ventricular bigeminy for 4 years with frequent bouts of ventricular tachycardia precipitated by either exercise or emotion (fig. 3). There had been no response to treatment with digitalis, quinidine, or guanethidine. With propranolol, 40 mg q.i.d., the exercise-induced ventricular tachycardia subsided, although ventricular bigeminy continued to occur intermittently. Therapy has now been maintained for 16 months with no adverse effects attributable to the drug.

Sinus Tachycardia

In three patients without demonstrable evidence of hyperthyroidism a persistent sinus

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**Figure 1**

*Effect of propranolol given orally to a patient with repetitive atrial tachycardia.*
Effect of propranolol given orally to a patient with paroxysmal A-V junctional tachycardia consistently precipitated by exogenous stimuli.

Effect of propranolol given orally to a patient with exercise-induced ventricular tachycardia.

tachycardia of over 100 beats per minute has been readily slowed with propranolol.

**Digitalis-Induced Arrhythmias**

Seven patients with arrhythmias due to digitalis intoxication (table 3) were treated with 10 mg of propranolol intravenously. Sinus rhythm was restored in all except two of these individuals by the end of the 10-minute infusion. In one patient ventricular tachycardia subsided, but pre-existent atrial flutter remained with a moderate ventricular response. In another patient, who had an ectopic atrial tachycardia, the ventricular response was slowed transiently but returned to its original rate within 5 minutes. Two patients with ar-

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*Circulation, Volume XXXIV, November 1966*
Table 3

Digitalis-Induced Arrhythmias Treated with Propranolol

<table>
<thead>
<tr>
<th>Type of Arrhythmia</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Ectopic atrial tachycardia</td>
<td>4</td>
</tr>
<tr>
<td>Multiple ventricular premature beats</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1</td>
</tr>
</tbody>
</table>

Arrhythmias due to digitalis became hypotensive after they were given intravenous propranolol. One of these patients also developed sinoatrial block. Both of these patients died and at postmortem examination both had pulmonary emboli.

Discussion

Considerable evidence now indicates that pronethalol, and undoubtedly also its cogener propranolol, have several modes of action on cardiac rhythm. Singer and associates\(^1\) have demonstrated that the sinus slowing, atrioventricular block, and depressed ventricular automaticity produced by pronethalol are probably mediated by beta-adrenergic blockade. However, the effects on the atria of increasing refractoriness, slowing of conduction, and depressing excitability appear to be due to direct muscular action and do not appear to be related to the neuroreceptors. Others\(^2\) have also suggested that pronethalol may have such a "quinidine-like" effect on the electrical properties of the myocardium. This latter action has been invoked as the mechanism whereby pronethalol reversed digitalis-induced arrhythmias, especially since its dextro-isomer (a compound 40 times less active in producing adrenergic beta-receptor blockade) similarly antagonized arrhythmias resulting from ouabain or acetylstrophanthidin.\(^3\) Taylor and Halliday,\(^4\) however, have suggested that this specific anti-arrhythmic effect may be related to a reduction in the amount of loss of intracellular potassium produced by the cardiac glycosides.

Many of these effects, particularly on heart rate and atrioventricular conduction, could not be reproduced by Wallace and co-workers\(^5\) in the unanesthetized dog with either proneth-

alol or propranolol. This is not consonant with clinical experience and the exact mechanisms of anti-arrhythmic action of these drugs thus remain unclarified. It is evident, though, that studies in animals with normal hearts cannot be directly related to patients with severe heart disease who are often receiving digitalis.

Slowing of the ventricular response to atrial fibrillation or to other supraventricular tachycardias as demonstrated in the present study and by others\(^6\) may be explained by blockade of adrenergic influences on the atrioventricular junction. Previous studies\(^7\) have indicated that depletion of myocardial noradrenaline stores results in a prolongation of the atrioventricular junctional refractory period. Neuroreceptor blockade would be expected to have a similar effect.

On the other hand, in three patients paroxysmal tachycardias which were consistently provoked by a variety of stimuli (Gallavardin's "tachycardie paroxystique à centre excitable")\(^8\) were prevented, rather than merely slowed, by propranolol. Since quinidine was previously ineffective in these patients, it is likely that propranolol abolished these arrhythmias by blockade of exogenous sympathethic stimuli to the heart. Slowing of clinically troublesome sinus tachycardias in three other patients may be similarly interpreted (table 1).

The direct depressant action of propranolol was demonstrated in the patient with repetitive tachycardia. A lengthening of the pauses between runs of rapid heart action (fig. 1) may be due to an effect on either impulse formation or impulse conduction in the atria.

In six of the seven patients with digitalis-induced arrhythmias the intravenous use of propranolol appeared both dramatic and specific. Indeed, the fact that only transient ventricular slowing occurred with propranolol in the seventh patient might imply that her ectopic atrial tachycardia was not engendered by digitalis. Further study is indicated to determine whether propranolol can be employed as a specific test of digitalis excess or toxicity as defined by Pick.\(^9\)
The occurrence of sino-atrial block in one subject after conversion of a digitalis-induced 2:1 atrial tachycardia to sinus rhythm may indicate that propranolol has little influence over the mechanism of sino-atrial block and that, therefore, this particular manifestation of digitalis excess became overt only after the previous arrhythmia had subsided. This explanation also might be construed in the patient with paroxysmal atrial flutter who had received large doses of digitalis and then, either fortuitously, or as a result of the addition of propranolol to sinus rhythm with sino-atrial block. Propranolol itself may cause marked sinus slowing either due to sino-atrial block or sinus standstill (cf. fig. 1); a block in the atria is a remote possibility for the slowing.

Since patients with cardiac arrhythmias are often seriously ill (especially those with digitalis excess or toxicity) and frequently manifest concomitant congestive heart failure, an anti-arrhythmic drug without adverse hemodynamic effects would be desirable. Unfortunately, propranolol, by virtue of its beta-adrenergic blocking activity, may impair myocardial function. Overt congestive heart failure developed in two patients, and significant hypotension occurred soon after the intravenous infusion of propranolol in three patients. That hypotension may have been due to an inhibition of cardiac beta-adrenergic neuroreceptors was evidenced in one subject by a prompt rise in the systemic blood pressure with isoproterenol.

In spite of this limitation, propranolol does have clinical application in certain selected disturbances of heart rhythm. It effectively slows the ventricular response in chronic or paroxysmal supraventricular tachycardias that are responsive to digitalis glycosides alone. This is presumably due to blockade of the beta-adrenergic contribution to A-V conduction. In addition, it is a useful agent in the prevention of paroxysmal tachycardias which are predictably induced by exogenous stimuli. Arrhythmias produced by digitalis are also responsive to propranolol, but careful clinical observation is mandatory since it may have an adverse effect in individuals with limited myocardial reserve.

Summary

The effects of intravenous and oral administration of propranolol, an adrenergic beta-receptor blocking agent, have been studied in 29 patients with various cardiac arrhythmias. The ventricular responses in chronic or paroxysmal supraventricular arrhythmias were decreased at rest or during exercise. Sinus tachycardias were regularly slowed. Two supraventricular tachycardias and one ventricular tachycardia, all consistently precipitated by exogenous stimuli, were prevented. Six instances of digitalis-induced arrhythmias were responsive to treatment.

Propranolol, especially when given orally, is of definite value in selected disturbances of cardiac rhythm. Reasonable caution should be exercised, however, because of the risk of precipitation of congestive heart failure or hypotension in patients with limited cardiac reserves.

References


Circulation, Volume XXXIV, November 1966

Sphinx

The fable adds very prettily that when the Sphinx was subdued, her body was laid on the back of an ass: for there is nothing so subtle and abstruse, but when it is once thoroughly understood and published to the world, even a dull wit can carry it. Nor is that other point to be passed over, that the Sphinx was subdued by a lame man with club feet; for men generally proceed too fast and in too great a hurry to the solution of the Sphinx's riddles; whence it follows that the Sphinx has the better of them, and instead of obtaining the sovereignty by works and effects, they only distract and worry their minds with disputations.—Selected Writings of Francis Bacon: Sphinx or Science. In The Modern Library. New York, Random House, 1955, p. 420.
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Circulation. 1966;34:767-773
doi: 10.1161/01.CIR.34.5.767

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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