Conservative Treatment of Chronic Heart Block

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Summary: A study of 203 patients with chronic heart block treated with oral long-acting isoprenaline showed that 85 (42%) were maintained satisfactorily on the drug for a mean period of 18.2 months. The survival rates at one, two, and three years were 76%, 64%, and 57% respectively. In 115 patients treatment by pacing became necessary to control symptoms, and in these patients the survival rates at one, two and three years were 83%, 72%, and 60%.

The two most valuable guides to patients' response to oral isoprenaline are the response to a trial dose of intravenous isoprenaline and the type of dysrhythmia associated with their Adams–Stokes attacks. Patients with heart failure with slow ventricular rates and those with angina of effort do not respond to treatment with sympathomimetic drugs.

The majority of patients with chronic heart block are elderly, and in view of the complexity of pacing systems, and the need for skilled supervision of paced patients, oral long-acting isoprenaline remains of value in the long-term management of chronic heart block, provided patients are carefully selected for this form of therapy.

Introduction

Numerous drugs have been used in the treatment of chronic heart block with Adams–Stokes attacks—adrenaline (Phear and Parkinson, 1922 ; Feil, 1923 ; Parkinson and Bain, 1924), ephedrine (Miller, 1925 ; Wood, 1932 ; Gilchrist, 1934), isoprenaline (Nathanson and Miller, 1952 ; Robbin *et al.*, 1955), and steroids (Friedberg *et al*, 1960 ; Dack, 1963 ; Aber and Wyn Jones, 1965).

The use of a long-acting preparation of isoprenaline was an advance (Robbin and Dack, 1959 ; Dack and Robbin, 1961 ; Fleming and Mirams, 1963 ; Bluestone and Harris, 1965), but its long-term results are not known. For this reason, and because of the increasing reliability of pacing systems, it has become necessary to re-evaluate what part, if any, drug therapy has to play in the long-term management of chronic heart block.

The results are reported of the use of oral long-acting isoprenaline in the treatment of 203 patients with symptoms from chronic heart block. Seventy-five of these patients formed the basis of the published data of Bluestone and Harris (1965), and since then long-acting isoprenaline has been used in a further 128 patients. In addition, the assessment of the value of the intravenous isoprenaline trial (Redwood, 1968) has been extended to include the results in 63 of these patients.

Long-Acting Isoprenaline

The preparation used (Saventrine) consisted of tablets containing cores of inert material coated with isoprenaline hydrochloride and covered with layers of ethyl cellulose—these granules were then compressed together into tablet form. The ethyl cellulose layers were designed to dissolve uniformly in the small gut to give continuous absorption of isoprenaline over a period of up to eight hours, though in practice it has been found necessary to give the drug at intervals of six hours or less in order to maintain an increased ventricular rate.

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Patients Studied

In the five years up to February 1968 long-acting isoprenaline has been used in the treatment of 203 patients (125 males and 78 females) with chronic heart block. Their ages ranged from 2 to 90 years, with a mean of 67.3 years, and the duration of symptoms (Table I) from 1 week to 13 years.

TABLE I.—*Presenting Symptoms in* 203 *Patients*

Adams–Stokes attacks	175	Angina of effort	27
Heart failure	59	Slow rate	1
Exertional dyspnoea	57	Basilar ischaemia	1
Dementia	2	Exhaustion	3

Of the 203 patients studied 175 (86%) presented with Adams–Stokes attacks, the underlying dysrhythmia being asystole in 39, ventricular tachycardia or fibrillation in 45, and sinoatrial arrest in 6. In the remainder (85) the rhythm in the attack was not known. The electrocardiographic findings in the 203 patients before starting long-acting isoprenaline are shown in Table II.

TABLE II.—*Electrocardiographic Findings in* 203 *Patients*

Sinus rhythm with intermittent heart block	41
Intermediate grades of heart block (2 : 1 and 3 : 1, etc.)	33
Complete heart block	129

Methods

In 63 of the 203 patients the effect of intravenous isoprenaline sulphate was observed in an attempt to predict the effect of oral long-acting isoprenaline (Redwood, 1968) and to avoid the risk of ventricular tachyrhythmias with long-acting isoprenaline. The drug was given in a concentration of 5 mg. of the sulphate diluted in 500 ml. of N saline or 5% dextrose by means of a conventional intravenous infusion set. (This gave a drug concentration of 10 μg. of isoprenaline per ml). The patients were monitored continuously on an oscilloscope while the infusion was started at less than 15 drops per minute (giving a dose of up to 10 μg of isoprenaline per minute). An E.C.G. was recorded at successive increases in drug concentration, the drip rate being increased until there was either an appreciable rise in ventricular rate (with 20 to 40 μg. of isoprenaline per minute) or arrhythmias appeared, in which case the infusion was stopped immediately.

Oral long-acting isoprenaline (Saventrine 30-mg. tablets) was usually given at an initial dose of 120 mg./day (30 mg. six-hourly), and increased (to a maximum of 300–360 mg./day) until the Adams–Stokes attacks were controlled. Some indication of the dose of oral long-acting isoprenaline needed was given by the response of the ventricular rate to intravenous isoprenaline—patients whose ventricular rate increased significantly on a small dose (<10 μg./minute) of intravenous isoprenaline would be likely to have a satisfactory rise in rate on a small dose of oral long-acting isoprenaline (120 to 180 mg./day), whereas patients who needed 10–15 μg./minute or more of intravenous isoprenaline to give a satisfactory rise in rate would

need higher doses of oral isoprenaline (200–300 mg./day) (Redwood, 1968).

Results

Intravenous Isoprenaline Test

The intravenous isoprenaline trial was used in 63 patients (Table III). Thirty-five had a stable increase in the ventricular rate—that is, a regular ventricular rhythm with up to 30 μg. of isoprenaline per minute—and 31 of these were maintained free from Adams–Stokes attacks on oral long-acting isoprenaline. Three of the remaining four patients continued to have Adams–Stokes attacks on oral long-acting isoprenaline ; the rhythm in the attacks was ventricular tachycardia or fibrillation. The other patient had ventricular ectopics on oral long-acting isoprenaline, and though he had no syncopal attacks he was paced.

TABLE III.—*Relation Between the Response to Intravenous Isoprenaline and the Response to Oral Long-acting Isoprenaline in 63 Cases*

Effect of Intravenous Isoprenaline	No. of Cases	Effect of Oral Long-acting Isoprenaline
Good response	35	31 No Adams–Stokes attacks 3 Adams–Stokes attacks continued 1 Ventricular ectopics
Poor response	13	12 Adams–Stokes attacks continued 1 No Adams–Stokes attacks
Variable response (intermittent heart block)	9	6 Adams–Stokes attacks continued 3 No Adams–Stokes attacks
Patients intolerant of intravenous or oral isoprenaline	6	5 Intolerable sinus tachycardia 1 Intolerable tremor and perspiration

Another four patients in this group of 35 were also paced ; they had had no syncopal attacks while taking long-acting isoprenaline, but two had refractory heart failure, one complained of excessive tiredness, and one had exertional dyspnoea.

Thirteen patients responded unsatisfactorily to intravenous isoprenaline, since a changing ventricular focus appeared with less than 30 μg./minute: 12 of them continued to have Adams–Stokes attacks on oral long-acting isoprenaline and only one remained free from attacks.

Nine patients had intermittent complete heart block, and the effect of intravenous isoprenaline on the rhythm was too variable to enable worth-while conclusions to be drawn. Six of these patients had to be paced because of continuing Adams–Stokes attacks on oral long-acting isoprenaline.

Side-effects prevented the proper evaluation of intravenous isoprenaline in six patients—five had an intolerable sinus tachycardia and one had tremor and excessive perspiration. These patients could not tolerate oral long-acting isoprenaline for the same reasons, and they were paced.

Intravenous isoprenaline was used in 14 additional patients, and, on the results, all but one were paced without a trial of oral long-acting isoprenaline. Eight had an unsatisfactory response to the infusion, with the production of ventricular arrhythmias at less than 30 μg. of isoprenaline per minute. (The rhythm in the Adams–Stokes attacks in these patients was ventricular tachycardia in six, asystole in one, and unknown in one.) Two patients continued to have asystolic episodes during the course of the infusion, two had intolerable sinus tachycardias, and one had intolerable tremor. The remaining patient had such infrequent syncopal attacks that he was not treated ; he was in sinus rhythm and intravenous isoprenaline had reduced the P–R interval from 0.25 to 0.16 second.

Long-term Treatment with Oral Long-acting Isoprenaline

Of the 203 patients treated with long-acting isoprenaline 85 (42%) were maintained on the drug for a mean period of 18.2 months (range 2 weeks to 56 months) and were not paced. Three patients discontinued long-acting isoprenaline after 3, 4, and 14 months ; one was unreliable at taking tablets, and in the other two sinus rhythm had returned with cessation of Adams–Stokes attacks. Forty-four of the 85 (52%) died after being on oral long-acting isoprenaline for a mean of 13 months (range 2 weeks to 43 months).

The remaining 115 patients were paced after being on oral long-acting isoprenaline for a mean of 3.9 months (range 3 hours to 30 months). The reasons for abandoning drug therapy are given in Table IV.

TABLE IV.—*Reasons for Discontinuing Oral Long-acting Isoprenaline in 115 Patients Who Were Paced*

Adams–Stokes attacks continued	84
Heart failure continued	34
Exertional dyspnoea continued	22
Long-acting isoprenaline produced ventricular fibrillation	2
Angina made worse by oral long-acting isoprenaline	1
Side-effects from oral long-acting isoprenaline:	
Palpitations	7 (2 ventricular ectopics, 5 sinus tachycardia)
Tremor	1

In order to determine which patients are likely to do well on oral long-acting isoprenaline the findings in the drug-controlled group are compared with the patients who were not controlled on drugs and needed pacing. Table V shows the results of this comparison in the 175 patients who presented with Adams–Stokes attacks. There is no significant difference in the ages and sex distribution in the two groups, but the patients who responded satisfactorily to long-acting isoprenaline tended to have had a longer duration of symptoms before treatment was started (mean 36.7 months) than those who subsequently needed pacing (mean 19 months). Analysis of the electrocardiographic findings was less helpful in predicting the response to oral long-acting isoprenaline than expected, and though the group of patients who needed pacing to control Adams–Stokes attacks contained a slightly higher percentage of cases with sinus rhythm, intermediate atrioventricular block, and left bundle-branch block, whether conducted or idioventricular, than the group of patients controlled on long-acting isoprenaline, the differences are not large enough to be of much help in planning treatment.

TABLE V.—*Analysis of 175 Patients With Adams–Stokes Attacks. The Findings in the Group of Patients Maintained on Oral Long-acting Isoprenaline are Compared With the Findings in the Group of Patients Paced After Failing to Improve on Oral Long-acting Isoprenaline. (Values in Parentheses are Percentages of Total)*

	Patients Maintained on Long-acting Isoprenaline	Patients Paced After Trial of Long-acting Isoprenaline
Total	72	103
Ages (years)	2–90 (mean 69·3)	14–89 (mean 66)
Duration of symptoms (months)	0·25–156 (mean 36·7)	0·5–156 (mean 19)
E.C.G.:		
Sinus rhythm	13 (19%)	27 (26%)
Intermediate A–V block	9 (13%)	15 (15%)
Complete A–V block	45 (61%)	58 (56%)
Atrial flutter or fibrillation with block	5 (7%)	3 (3%)
Narrow QRS (<0·08)	12 (17%)	15 (15%)
Bundle branch block Right	49 (67%)	63 (61%)
Bundle branch block Left	11 (16%)	25 (24%)
Rhythm in Adams–Stokes attacks:		
Asystole	17 (24%)	21 (20%)
Ventricular tachycardia or fibrillation	9 (12%)	37 (36%)
Sinoatrial arrest	1 (1%)	4 (4%)
Unknown	45 (63%)	41 (40%)

Knowledge of the dysrhythmia in the Adams–Stokes attack was of some value in predicting the response to oral long-acting isoprenaline, since the majority of patients with attacks due to ventricular tachyrhythmias were not controlled on long-acting isoprenaline and needed pacing (Table V), but the most helpful pointer to the patient's response to long-acting isoprenaline proved to be the intravenous isoprenaline trial (Table III).

The effect of oral long-acting isoprenaline on symptoms other than Adams–Stokes attacks is shown in Table VI. Half of the 51 patients with heart block who presented with exertional dyspnoea but with no clinical or radiological evidence of heart

TABLE VI.—*Effect of Long-acting Isoprenaline on Symptoms other than Adams–Stokes attacks*

	Exertional Dyspnoea. 51 Patients		Heart Failure. 56 Patients		Angina of Effort. 16 Patients		Dementia. 2 Patients	
	Improved	No Change	Improved	No Change	Improved	No Change	Improved	No Change
Long-acting isoprenaline	18	18	0	18	0	13	0	2
Long-acting isoprenaline + diuretic	5	1	1	7	0	1	—	—
Long-acting isoprenaline + diuretic + digitalis	3	6	13	17	0	2	—	—
Total	26	25	14	42	0	16	0	2

A few patients were not treated with long-acting isoprenaline long enough for the effect of isoprenaline to be observed—they were paced because of continued Adams–Stokes attacks. This explains the discrepancy between the totals in this table and Table I.

failure at rest, were improved on long-acting isoprenaline—there was no obvious change in the other half. None of the 56 patients with heart failure (raised jugular venous pressure or pulmonary venous congestion) associated with slow ventricular rates showed any appreciable response to isoprenaline, and there was significant improvement in only 13 after digitalis and diuretics had been added. Twenty-seven patients, in addition to other symptoms, presented with angina of effort. Eleven of them had too short a trial of oral long-acting isoprenaline to be able to judge the effect on the ischaemic pain, but none of the remainder (16) noticed any improvement on isoprenaline—in fact, in one patient the angina was made worse by isoprenaline.

Discussion

Survival of Patients with Heart Block

The survival of patients with chronic heart block has been variously estimated by different authors. Campbell (1944), in his study of 50 patients presenting with symptoms due to complete heart block and with adequate follow-up data, found that 34 had died in a mean time of 2.5 years. Penton *et al.* (1956) studied 224 patients with symptoms due to complete heart block. Excluding those patients with block associated with acute myocardial infarction, the mean survival after the first syncope in 59 patients who died was 43.6 months. Rowe and White (1958) extended the study of Graybiel and White (1936), and from 160,000 electrocardiograms taken at the Massachusetts General Hospital from 1925 to 1955 found 261 cases adequately documented, with complete heart block in one or more tracings.

A more realistic approach to the problem of presenting survival results was made by Johansson (1966), who studied the one-year prognosis of 193 patients in Malmo with documented evidence of complete heart block. The one-year survival of these patients, excluding 60 with heart block associated with acute myocardial infarction, was 56.2%. Johansson's material for this prognostic study was obtained from electrocardiographic files and therefore probably included some heart block patients without symptoms. In addition, no details of treatment were given.

Of our 85 patients maintained on oral long-acting isoprenaline without pacing the one-year survival was 75.6%, the two-year survival 64.3% (56 patients), and the three-year survival 57% (28 patients).

It can be assumed that the majority of patients in published data on heart block have received drug therapy designed to prevent Adams–Stokes attacks, and if the attacks are successfully abolished survival will largely depend on the aetiology of the heart block and its rate of progression, this being uninfluenced by any form of therapy currently available. The success of therapy, therefore, may be judged by its ability to prevent life-threatening Adams–Stokes attacks. Here lies the great difficulty in judging success of drug therapy in controlling Adams–Stokes attacks, for the variation in frequency of attacks in untreated chronic heart block makes assessment difficult. The number of patients in the present study may, however, be considered sufficient to allow valid conclusions.

How does long-acting isoprenaline compare with artificial pacing? The one-, two-, and three-year survival rates for a

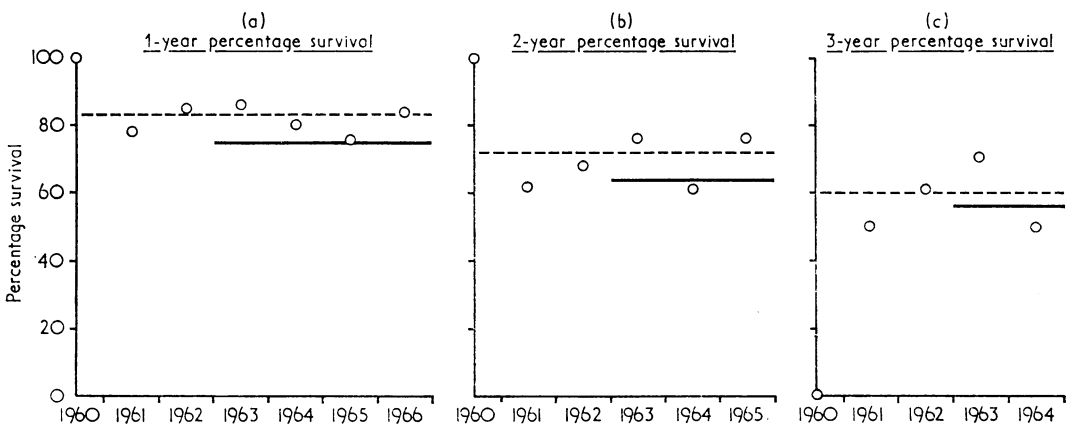

FIG. 1.—One-, two-, and three-year survival rates. This shows the percentage of patients alive at the end of one, two, and three years of pacing (broken line) or long-acting isoprenaline (continuous line). The circles show the annual results for the paced patients.

Of these patients, 187 had heart block assumed to be due to coronary artery disease or rheumatic heart disease, and the mean survival in these was 55.1 months. In the present study of 203 patients it has been assumed that the onset of symptoms usually coincided with the onset of heart block. The mean survival (duration of symptoms + duration of drug therapy) in the 44 patients who died on oral long-acting isoprenaline was 43.2 months. Results such as these may be misleading, since they refer only to the patients who have died, thus giving an unfavourable bias to the figures.

total of 156 patients paced for symptoms due to chronic heart block at St. George's Hospital before February 1967 are 83%, 72%, and 60%, which shows a significantly better result with this form of therapy at the one- and two-year level and similar results to the drug-controlled group at the three-year level (Fig. 1). It should be appreciated, however, that the patients who were paced do not form a comparable group to the patients on long-acting isoprenaline, since the majority were paced only after long-acting isoprenaline had failed to control symptoms, and these would therefore form a poorer-risk group of patients.

It is likely that with increasing reliability of pacing systems the pacing survival rates will improve further, but pacing systems need highly skilled medical and technical staff and complex equipment for installation and maintenance. For these reasons and because we are dealing with an elderly group of patients, often suffering from additional disease, there is still a place for the use of drugs in the treatment of chronic heart block provided patients are carefully selected for this form of therapy.

Selection of Patients for Treatment

Patients with a long duration of symptoms are more likely to do well on drugs than those with a short history. This cannot be explained by the underlying aetiology, since the length of history gives no clue to the cause of chronic heart block (Harris *et al.*, 1968), but it may be due to the block becoming complete, with less liability to rhythm changes, after a long period of time. The use of a preliminary trial of intravenous isoprenaline has proved a valuable indicator of the likely result of long-term treatment with oral long-acting isoprenaline, and is also of value in avoiding the risk of ventricular tachyrhythmias with long-acting isoprenaline. The majority of patients who have a stable increase in ventricular rate with intravenous isoprenaline will do well on long-acting isoprenaline, and those who have a changing ventricular focus with modest doses of intravenous isoprenaline will respond poorly to oral therapy (Table III). Knowledge of the dysrhythmia in the Adams–Stokes attacks is also of some value in deciding treatment. As expected, patients with ventricular tachyrhythmias usually respond less well to drug therapy than those with attacks due to asystole. Improvement in monitoring systems to record the attack rhythm in a greater percentage of patients may make this correlation closer.

The electrocardiographic changes have proved less helpful than expected in deciding treatment. About one-third (74) of the 203 patients studied were in sinus rhythm or intermediate heart block (2 : 1, 3 : 1, etc.) (Table II). There were more patients with these lower grades of block in the group needing pacing to control symptoms (42 of 103, 41%) than in the group which did well on oral long-acting isoprenaline (22 of 72, 30%), but the difference was not great. While these results tend to confirm the belief that patients with intermittent or incomplete heart block respond less well to drug therapy and commonly need pacing to control symptoms, some remain well on drugs. Most of the patients in sinus rhythm tolerated isoprenaline surprisingly well and only five needed pacing because of intolerable sinus tachycardia produced by the drug. The other 24 patients with sinus rhythm were paced because of continued Adams–Stokes attacks (Table V).

Heart failure with slow ventricular rates responds poorly to isoprenaline (with or without the addition of digitalis in those patients in complete heart block (Table VI). The majority of these patients need artificial pacing to increase the ventricular rate sufficiently. Angina of effort does not improve with the use of isoprenaline and may be made worse, since cardiac work and oxygen consumption are increased.

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Asymptomatic Urinary Tract Infection in Gynaecological Outpatients

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Summary : In this study mid-stream specimens of urine were collected from all new patients attending a gynaecological outpatient department and tested for significant bacteriuria. Those having an asymptomatic infection were followed up, treated, and investigated radiologically.

Of 1,506 women screened for bacteriuria 82 (5.4%) were found to have a persistent infection. The predominant organism was Escherichia coli, present in 83% of infections. Treatment with sulphonamides produced a good cure rate, which was improved by ampicillin given to failures. Some patients, however, had infections that persisted or recurred despite several antibiotics. The radiological investigations showed that a high proportion of women with asymptomatic urinary infection had severe renal disease which was quite symptomless. This was more pronounced in those with persistent or recurrent infections.

Introduction

The presence of a significant bacteriuria, defined as over 100,000 or more organisms per ml. of urine (Kass, 1956), has been found to occur in 5% of pregnant women and to be equally or more prevalent among diabetics, elderly patients, and some other population groups. In pregnancy this bacteriuria is often associated with renal abnormality (Kincaid-Smith and Bullen, 1965) and is usually asymptomatic.

We have studied women attending a gynaecological outpatient department to find the incidence of asymptomatic infection present in this group of patients, to determine if any

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