PAPERS AND ORIGINALS

Long-term Beta Blockade: Possible Protection from Myocardial Infarction

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British Medical Journal, 1975, 1, 117-119

Summary

The clinical behaviour of 90 patients on beta-blocking drugs for established coronary heart disease who were admitted to a coronary care unit with prolonged ischaemic myocardial pain was compared with that of 90 similar patients not on this therapy. Transmural myocardial infarction was confirmed in 30 of the patients on beta-blockers and in 62 controls. A diagnosis of myocardial necrosis without infarction was made in 20 patients on beta-blockers and in 14 controls. Coronary insufficiency was diagnosed in 40 patients on beta-blockers and in 14 controls. The incidence of sinus bradycardia, hypotension, syncope, and radiological pulmonary oedema was similar in the two groups.

Established beta-blockade, therefore, has not been shown to prejudice the outcome of patients with coronary heart disease admitted to hospital with prolonged ischaemic myocardial pain. On the contrary, it may protect some patients from the development of a myocardial infarction.

Introduction

Many patients with established coronary heart disease who enter coronary care units with a prolonged attack of ischaemic myocardial pain are on beta-blockers. From a theoretical standpoint it might be expected that this group of patients would be more prone to cardiac failure, syncope, hypotension, and bradycardia at a time when their coronary blood flow was compromised.

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A retrospective analysis of 452 patients admitted to the coronary care unit, Kingston General Hospital, Hull, with ischaemic myocardial pain from 1 July 1971 to 30 June 1972 showed that 52 patients were being treated with beta-blockers before admission. A diagnosis of acute myocardial infarction was made in only 22 (42%) of these patients whereas this diagnosis was established in 275 (69%) of the remaining 400 patients who were not on beta-blockers. The incidence of radiological pulmonary oedema, sinus bradycardia, and syncope was similar in both groups. These observations suggested that beta-blockade in coronary artery disease with stable angina might protect against acute myocardial infarction. A prospective study was therefore designed to see whether these initial uncontrolled observations could be substantiated.

Patients and Methods

All 341 patients who were admitted to the coronary care unit with a prolonged attack of ischaemic myocardial pain between 15 September 1972 and 19 October 1973 were studied. Data forms were designed to separate the basic information (age, sex, previous cardiac history, medication before admission, and duration of the chest pain which had caused referral to the unit) from the clinical progress and final diagnosis. In this way the selection of control patients was achieved without bias with regard to the final diagnosis (acute myocardial infarction, myocardial necrosis without infarction, and coronary insufficiency). No attempt was made to assess the severity of the angina as this is renowned to be both difficult and inaccurate. The patients studied formed two groups.

Beta-blocker Group.—This group consisted of 90 patients who had experienced symptoms of ischaemic heart disease for at least three months and had been treated by beta-adrenergic blockade for more than a month. The minimum drug dosage for inclusion in this group was propranolol 20 mg, oxprenolol 40 mg, or practolol 100 mg three times a day. All patients were asked whether they had been taking the medication as prescribed. Beta-blockers were immediately withdrawn when the patients entered the coronary care unit.

Control Group.—Of the remaining 251 patients the first consecutive 90 who matched the beta-blocker group in age, sex, previous cardiac history, and the duration of the chest pain

which had caused their referral to hospital were selected as controls (without knowledge of their clinical progress or of the final diagnosis).

DEFINITIONS

The diagnosis of acute anterior and posterior myocardial infarction was based on the electrocardiographic (E.C.G.) criteria of the World Health Organization (1959). The recommendations of Perloff (1964) were used to define "true" posterior infarction. When the site of infarction was obscured by pre-existing E.C.G. abnormalities (previous myocardial infarction and/or left bundle branch block) a diagnosis of recent infarction was made on the basis of a characteristic history, a raised peak serum aspartate aminotransferase (SGOT) level, a typical temperature curve, and a raised sedimentation rate (Marriott *et al.*, 1973).

Myocardial necrosis without localized infarction was diagnosed in those patients with raised serum enzymes who also developed persistent S-T segment and T-wave changes, other causes of raised serum enzymes having been excluded.

The diagnosis of coronary insufficiency was made in the presence of typical ischaemic cardiac pain without E.C.G. or enzyme evidence of recent infarction or necrosis.

E.C.G.s were recorded on each of the first three days of the patients' stay in the coronary care unit and weekly thereafter unless there was an indication for obtaining further records.

The SGOT was estimated daily for at least the first three days then weekly. The first sample was drawn on the day of admission. SGOT was measured by a modified spectrophotometric method using a reaction rate analyser. The upper limit of normal for our laboratory was 22 IU and the SGOT was considered abnormal if 10% above this limit.

Left heart failure was defined as radiological pulmonary oedema. Lesser degrees of pulmonary congestion were excluded as the amount of observer error (clinical and radiological) in this condition is great.

Statistical analysis of the data was made using the χ^2 test for two independent samples and the Fisher test of exact probabilities.

Results

The incidence of myocardial infarction, myocardial necrosis without infarction, and coronary insufficiency is shown in

TABLE II—Incidence of Cardiac Failure in Beta-blocker and Control Groups

Diagnosis	Beta-blocker Group			Control Group		
	No. of Patients	No. with Early Heart Failure*	No. with Late Heart Failure†	No. of Patients	No. with Early Heart Failure*	No. with Late Heart Failure†
Myocardial infarction	30	11	5	62	15	11
Myocardial necrosis without infarction	20	4	1	14	4	2
Coronary insufficiency	40	1		14		
Total	90	16	6	90	19	13

*Early, less than 72 hours from time of admission to coronary care unit.

†Late, more than 72 hours from time of admission to coronary care unit.

TABLE III—Incidence of Arrhythmias in Beta-blocking and Control Groups. Results are Numbers of Patients

Arrhythmia	Beta-blocker Patients with:				Control Patients with:			
	Myocardial Infarction	Myocardial Necrosis without Infarction	Coronary Insufficiency	Total	Myocardial Infarction	Myocardial Necrosis without Infarction	Coronary Insufficiency	Total
Ventricular fibrillation/ventricular tachycardia	6			6	11			11
Supraventricular tachycardia	7	7	1	15	10	3		13
Ventricular ectopics	4		1	5	8		1	12
Ventricular asystole	6			6	8			8
Complete heart block	2			2	4			4

table I. Myocardial infarction occurred more often in the control group than in the beta-blocker group ($P < 0.001$). Conversely, the incidence of coronary insufficiency in the beta-blocker group was significantly greater than in the control group ($P < 0.001$). The occurrence of myocardial necrosis without infarction was the same in the two groups. In each group the proportion of patients with myocardial infarction, myocardial necrosis without infarction, and coronary insufficiency who were receiving either propranolol or practolol was similar. The number of patients on oxprenolol was too small for adequate comparison.

TABLE I—Incidence of Myocardial Infarction, Myocardial Necrosis without Infarction, and Coronary Insufficiency in Beta-blocker and Control Groups. Results are Numbers (%) of Patients

Group	Myocardial Infarction	Myocardial Necrosis without Infarction	Coronary Insufficiency	Total
Patients on beta-blockers	30 (33)	20 (22)	40 (45)	90 (100)
Control patients	62 (69)	14 (15.5)	14 (15.5)	90 (100)

The incidence of cardiac failure and arrhythmias are shown in tables II and III. While these complications occurred with equal frequency in patients in both groups who had suffered recent myocardial infarction the total number of cases of late cardiac failure and major arrhythmias (ventricular tachycardia, ventricular fibrillation, asystole, and complete heart block) was greater in the control group ($P = 0.03$, $P < 0.05$ respectively).

Death occurred in nine patients in the beta-blocker group and in 10 controls. Within the beta-blocker group the mortality did not seem to be related to drug dosage, recognizing that the number of patients receiving each drug was small.

Six patients on beta-blockers and four controls had had syncopal episodes before admission, but this was not statistically significant. Fifteen patients on beta-blockers and 12 in the control group had sinus bradycardia (pulse rate less than 50/min).

TABLE IV—Peak SGOT Levels in Beta-blocker and Control Groups. Results are Numbers of Patients

Peak SGOT Levels (IU):	<24	24-99	100-199	200-500	>500
Patients on beta-blockers	40	24	9	13	4
Control patients	14	31	15	16	14

TABLE V—Time between Onset of Pain and Admission to Coronary Care Unit. Results are Numbers (%) of Patients

Time (Hours)	Beta-blocker Patients with:			Control Patients with:		
	Myocardial Infarction	Myocardial Necrosis without Infarction	Coronary Insufficiency	Myocardial Infarction	Myocardial Necrosis without Infarction	Coronary Insufficiency
<4	7 (23)	5 (25)	13 (32.5)	21 (33)	6 (43)	3 (21)
4-12	10 (33)	8 (40)	7 (17.5)	20 (33)	2 (14)	5 (37)
13-24	9 (30)	6 (30)	6 (15)	10 (16)	2 (14)	3 (21)
>24	4 (14)	1 (5)	14 (35)	11 (18)	4 (29)	3 (21)
Total	30 (100)	20 (100)	40 (100)	62 (100)	14 (100)	14 (100)

The peak SGOT levels of the two groups are shown in table IV. They were higher in the control group.

There was no significant difference in the time of onset of pain to admission to the coronary care unit (table V), the systolic blood pressure, or pulse rate on admission between the two groups ($P > 0.05$).

In both groups the incidence of myocardial necrosis (with or without infarction) in patients with a previous history of infarction was not significantly different from those without prior infarction.

Discussion

Beta-receptor antagonists are widely used and of proven benefit in the therapy of angina pectoris (Gillam and Prichard, 1966; Elliott and Stone, 1969; George *et al.*, 1970). Though the mode of action of these drugs has not been completely elucidated it seems likely that some of their therapeutic effect is due to reduction in myocardial oxygen consumption as a consequence of a decrease in heart rate and mean systolic blood pressure (Taylor, 1973). They may also be expected to slow the velocity of myocardial contraction as a sequel to blocking the inotropic receptors in the myocardium (Sonnenblick *et al.*, 1965). In clinical practice the level of sympathetic overdrive in a patient with prolonged ischaemic myocardial pain is difficult to assess. Nonetheless, it seems probable that establishing beta-blockade in such patients could be of benefit and recently the Boston Group have shown that propranolol was usually rapidly effective in relieving the features of acute myocardial ischaemia in the intermediate coronary syndrome (Fischl *et al.*, 1973). It is therefore improbable that beta-blockers could prolong ischaemic pain by causing coronary spasm (Carleton and Johnson, 1974).

In patients with stable angina it has not yet been shown that beta-blockers protect against myocardial infarction, but this may be the explanation of our results provided that the control group of patients is acceptable.

In spite of the prediction that in patients on beta-blockers

there would be an increased incidence of cardiac failure, syncope, hypotension, and bradycardia after prolonged ischaemic myocardial pain this was not shown. The greater frequency of late cardiac failure and major arrhythmias in the control group is in accordance with the higher incidence of myocardial infarction in this group.

The similar mortality rate in the two groups suggests that a myocardial infarction sufficiently extensive to be fatal was not prevented by beta-blockade.

In view of the relatively short half life of the beta-blockers (Carruthers *et al.*, 1973) their immediate withdrawal after the patients' entry to hospital may explain why there was no observed reduction in the incidence of arrhythmias in patients who had suffered either myocardial necrosis (with or without infarction) or coronary insufficiency.

Established beta-blockade, therefore, in no way prejudices the outcome of patients admitted to hospital with prolonged ischaemic pain. On the contrary, it may protect some patients from the development of myocardial infarction and so enhance their long-term prognosis.

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