Clinical, electrocardiographic, and haemodynamic effects of long-term use of propranolol in Prinzmetal's variant angina pectoris

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A long-term administration of propranolol in 5 patients with Prinzmetal's angina pectoris was highly successful. The effect of the drug was evaluated on a clinical, electrocardiographic, and haemodynamic basis. In 4 patients the complete disappearance of the subjective symptoms, of the electrocardiographic alterations occurring during the anginal attacks, and of the associated haemodynamic changes was achieved. In one patient the anginal episodes became obviously less frequent and severe.

The haemodynamic study showed that: (a) the attacks were not secondary to circulatory modifications which acutely increase work or oxygen consumption of the heart; (b) no pattern could be established for the success of the drug as regards the changes induced on the basal blood pressure, left ventricular work, and tension time index; (c) cardiac function was remarkably improved in each patient after propranolol administration. These observations can hardly be explained with the commonly suggested mechanism of action of propranolol in angina pectoris.

A long-term follow-up ranging from 4 to 17 months confirmed the favourable effects observed in the first weeks of treatment.

The effects were strictly dose dependent and optimal results were achieved at individualized doses.

Convincing evidence exists that the administration of propranolol, a beta-adrenergic blocking agent, in angina pectoris is generally followed by a favourable therapeutic response (Keelan, 1965; Gillam and Prichard, 1966; Ginn and Orgain, 1966; Hamer and Sowton, 1966; Gianelly *et al.*, 1967; Hebb, Godwin, and Gunton, 1968; Amsterdam, Gorlin, and Wolfson, 1969). The basis for the treatment of angina pectoris by beta-blockers may be viewed in terms of the pathophysiology of angina pectoris and its relation to cardiac adrenergic stimulation. Angina pectoris is thought to be the result of an imbalance between myocardial oxygen demand and supply (Gorlin, 1965). This disparity may be worsened by adrenergic stimuli which increase myocardial mechanical effort and consequently the oxygen demands of the heart. Beta-adrenergic blockade results in a reduction of

several of the major determinants of myocardial oxygen consumption through a decrease of heart rate, velocity of contraction, and cardiac work (Wolfson *et al.*, 1966; Epstein *et al.*, 1965; Sonnenblick *et al.*, 1965; Robin *et al.*, 1967; Wolfson and Gorlin, 1969). This provides a reasonable explanation of the favourable effects of propranolol in those anginal episodes in which catecholamine stimulation, namely during emotional stress or physical exercise, occurs.

The attacks of a variant form of angina, as described by Prinzmetal *et al.* (1959), occur at rest and are not related to the common eliciting factors. A recent haemodynamic study carried out by our group (Guazzi *et al.*, 1971) showed that the typical electrocardiographic modifications of this form of angina are not preceded and, consequently, not triggered by any change in the major circulatory parameters, such as heart rate, arterial pressure, cardiac output, or duration of the left ventricular ejection time, all of which interfere with work or oxygen requirement of the heart.

Received 10 March 1971.

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It is difficult, therefore, to interpret these anginal attacks on the basis of classical pathophysiology.

For these reasons, the evaluation of the effects of propranolol in this form of angina appeared worthy of investigation. We report our observations, both for the practical importance that they may assume, especially if confirmed by other workers, and for the theoretical interest of questions raised about the pathogenesis of this form of angina, the mechanism of action of propranolol in preventing anginal attacks, and the effects of this drug on cardiac function and systemic circulation of patients with Prinzmetal's angina.

Methods

Five patients, four men and a woman, were investigated. All of them had a history and an electrocardiographic pattern (Guazzi *et al.*, 1970) typical of the variant form of angina (Prinzmetal *et al.*, 1959). Their electrocardiographic features are shown in Fig. 1. The basal electrocardiogram (Fig. 1A) was normal in Case 1. In Case 2 it showed an old myocardial infarction and left ventricular hypertrophy. In the other two men (Cases 3 and 4) it revealed recent infarction of the diaphragmatic and anteroseptal myocardial areas, respectively. In both patients infarct occurred a few days before admission. The basal electrocardiogram of the woman (Case 5) showed left axis deviation and negative T waves in the inferior leads.

The subsequent steps of the investigation were arranged as follows. (a) Daily charting, throughout the hospital period, of the number, time, and circumstances of the anginal attacks. (b) Continuous electrocardiographic recording during many hours after the first week of stay in the hospital. (c) Haemodynamic study during the day after the continuous recording of the electrocardiogram. (d) Oral administration of propranolol continued for several days. (e) Repeat of the haemodynamic study after periods of treatment ranging from 13 to 31 days.

Daily recording of the anginal episodes indicated the hours of the day when spontaneous angina occurred most often for each patient. Both the electrocardiographic and the haemodynamic studies were carried out during these hours, and lasted 7 hours for Case 1, 6 hours for Cases 2 and 5, and 5 hours for Cases 3 and 4, respectively.

During the electrocardiographic sessions, the four leads which presented the most evident changes were continuously recorded, according to the method previously described (Guazzi *et al.*, 1970). During the episodes of angina (Fig. 1B) Cases 1, 2, 3, and 5 showed conspicuous ST segment elevation with reciprocal depression in the peripheral leads; in Case 4 the ST tract elevation occurred in the precordial leads, from V₂ to V₅.

During the haemodynamic studies, the electrocardiographic lead showing obvious ST segment and T wave changes, heart rate, arterial pressure,

and right atrial pressure were continuously recorded. Left ventricular ejection time and isovolumic contraction time were also measured according to the method indicated by Weissler, Harris, and Schoenfeld (1968). Cardiac output was determined at selected times. Systemic peripheral resistance and the mean rates of isovolumic pressure development and systolic ejection were calculated (for details, see Guazzi *et al.*, 1971). Left ventricular minute work was obtained as the product of mean arterial pressure and cardiac index; the tension time index per minute was calculated as the product of the mean systolic arterial pressure, the left ventricular ejection time, and the heart rate.

The patients were instructed, during the entire

FIG. 1 Two electrocardiographic leads of each of the 5 patients recorded in the absence of pain (A), during severe spontaneous pain (B), and 2 minutes after the pain had subsided (C). Note the ST tract elevation and the reciprocal depression in the peripheral leads in Cases 1, 2, 3, and 5.

duration of the pain, to keep pressed a button for the remote control of a marker of the recording system. This provided a good time relation between pain and electrocardiographic and circulatory events.

Propranolol was given orally in an initial daily dosage of 40 mg, which was subsequently increased according to the patient's response. The increment was 40 mg every other day. The final dose was individualized to achieve, when possible, complete relief of the angina. The doses of 40 mg were uniformly distributed during the 24 hours. In Case 2 the large daily amount of propranolol (480 mg) was fractionated in doses of 80 mg. In 4 patients complete relief of the angina was achieved. The haemodynamic control was repeated only after one week of complete absence of anginal pain reports in the patient's charting. All the subjects were discharged under propranolol treatment at the individual doses which had induced optimal therapeutic effect. A long-term follow-up was then begun.

Results

Clinical and electrocardiographic effects

The ST segment modifications appropriate to this form of angina are so obvious in their waxing, steady, and waning phases as to make unequivocal their identification during continuous electrocardiographic recording. As already mentioned, during the haemodynamic studies, together with the various circulatory parameters, the electrocardiographic lead showing the most obvious changes during the anginal episodes was recorded. The circulatory sessions, therefore, also provided reliable information about the patients' electrocardiographic behaviour. The continuous electrocardiographic recording revealed the occurrence of an almost equal number of episodes

of ST segment elevation accompanied by pain, and of episodes with very similar electrocardiographic modifications without the patient experiencing any disturbance. It is not surprising, therefore, that recorded episodes of ST changes during the studies were more frequent than the pains charted by the patients in the 24 hours.

Complete relief of anginal symptoms and of electrocardiographic alterations occurred in 4 patients. Of particular interest is the disappearance not only of the ST segment changes accompanied by pain, but also of those unaccompanied by pain.

A dose-dependent effect was noted in all the cases. In one patient (Case 3), who before beta-blockade had bradycardia (55/min) at rest, the increment of propranolol was interrupted at a dose of 120 mg/day, which brought the heart rate to 50/min. Though this dose did not completely abolish the painful attacks, it reduced their frequency from 8 to 12 to 1 to 2 in the 24 hours. None of these occurred during the circulatory study after propranolol.

No change in the basal electrocardiographic aspect was detected after treatment. No remarkable side effect was observed.

Haemodynamic effects In a previous paper (Guazzi *et al.*, 1971) haemodynamic changes associated with episodes of electrocardiographic abnormality were reported. One patient (Case 5), who was investigated after that paper was published, behaved in a similar manner to the other 4 subjects. The major observations can be summarized as follows. (a) In none of the recorded anginal episodes did haemodynamic changes precede the electrocardiographic abnormalities: the

TABLE Circulatory parameters before (upper lines) and after (lower lines) beta-blockade

Case No.	Propranolol dose (mg/day)	Heart rate (beats/min)	Mean arterial pressure (mmHg)	Mean rt. atrial pressure (mmHg)	Cardiac index	Systemic periph. resistance (dynes sec cm ⁻⁵)	LV ejection time (msec)	Mean syst. ejection rate (ml/sec/m ²)	Isovol. contraction time (msec)	Mean rate isovol. pressure develop. (mmHg/msec)	Dye mean transit time (sec)
1	240	66	106	2.7	2075	2070	270	116	55	1.4	18
		57	123	1.7	3300	1516	348	166	47	2.1	17
2	480	90	88	2.3	3736	964	264	157	46	1.5	14.5
		75	92	2.3	4384	860	310	188	28	2.5	14
3	120	55	91	2.3	2873	1418	320	163	60	1.1	20
		50	88	2	3247	1217	340	191	30	2.3	20
4	160	88	115	1	4206	1313	270	176	55	1.6	16
		70	103	1	4636	1065	290	228	30	2.8	15
5	200	78	100	3	2070	2204	300	88	50	1.4	18
		57	106	3	1820	2658	340	104	35	2	17.5

former always began simultaneously with the latter. (b) No major qualitative difference was detected between the 45 recorded attacks and no qualitative difference was evident between the episodes with and those without pain. (c) The obvious decrease in arterial pressure, cardiac output, mean rates of isovolumic pressure development and systolic ejection, the increase of right atrial pressure, and the lengthening of the dye appearance time and isovolumic contraction time observed during the phases of ST segment elevation, both in the presence and in the absence of pain, indicated the occurrence of remarkable left ventricular impairment.

After beta-blockade, parallel with the electrocardiographic pattern, no circulatory variation was observed throughout the haemodynamic sessions. Therefore, not only were the electrocardiographic abnormalities abolished, but also the associated haemodynamic changes.

In the Table a comparison is made between the basal circulatory parameters before beta-blockade, and the circulatory values observed after treatment with propranolol. The following modifications in systemic circulation were detected: a constant decrease in the heart rate, non-uniform changes in arterial pressure, an increase in cardiac output, and a decrease in the systemic peripheral resistance in 4 patients, a decrease in the former and an increase in the latter in one patient. Of the various parameters reported in the Table, the duration of the isovolumic contraction time (Weissler *et al.*, 1968), the mean systolic ejection rate (Braunwald, Sarnoff, and Stainsby, 1958), and the mean rate of isovolumic pressure development (Gleason and Braunwald, 1962; Jezek, 1966), are those that closely depend on cardiac function. After beta-blockade these parameters showed the following changes in all patients. The isovolumic contraction time became shorter, and the mean rates of isovolumic pressure development and of systolic ejection were remarkably enhanced. The right atrial pressure and the circulation time (here expressed by the dye mean transit time), also related to cardiac function, remained unchanged or slightly decreased.

After propranolol administration left ventricular work increased in 3 subjects and was moderately reduced in 2; tension time index fell in 3 patients and was augmented in 2 (Fig. 2).

Long-term follow-up The 5 patients (Cases 1-5) were investigated after periods varying from 3 months to 1 year.

Case 1 Three months after returning home he developed pneumonia. He consulted his private doctor and was given penicillin. He died suddenly 10 minutes after the injection. Apparently he had never had penicillin before. Necropsy was not performed and the cause of death was not determined. In the three months after discharge from hospital he had continued to take propranolol at the same dose administered in the hospital (240 mg/day) and had remained completely free of symptoms.

Case 2 He was discharged on a daily dose of 480 mg propranolol. Because he did well in the following two months, a progressive reduction of the dose was tried. Anginal pains reappeared when the dose was 280 mg/day. Propranolol was then administered in doses of 80 mg four times daily and in the past 15 months the patient has been asymptomatic except for very rare (twice a month or less) and mild episodes of pain which never required nitroglycerin. Gradually, restrictions of his activities have been reduced. No side effect has been observed apart from moderate sleeplessness.

Case 3 During a one-year follow-up he has been taking 120 mg a day of propranolol. He is still suffering mild and short episodes of substernal pain at rest, 3 to 4 times a week. Because of permanent bradycardia, larger doses of beta-blocker could not be administered during this time. A temporary discontinuance of the drug induced a striking increase both in the frequency and severity of the anginal attacks. Three months after discharge from hospital he was able to return to his normal occupation. Except for bradycardia, no untoward effect has been noted.

Case 4 In this patient the initial dose of propranolol (160 mg/day) was tapered and discontinued after five months. He has gradually increased his activities and has remained free of symptoms except for vague, mild, intermittent chest discomfort during the past 10 months.

FIG. 2 Left ventricular work (LVW) and tension time index (TTI) in the patients in the control phase (C) and after treatment with propranolol (P).

Case 5 In the four months during which she had been taking 200 mg a day of propranolol she was free of symptoms. Recently, because of diarrhoea, her private doctor discontinued the drug. Anginal pains reappeared so frequently and severely as to require the use of narcotics. The patient has been admitted again to hospital. The electrocardiogram recorded for many hours showed, during the anginal episodes, the same pattern described previously and shown in Fig. 1. Beta-blockade was restored and complete relief of angina was achieved.

Discussion

The use of propranolol appeared highly successful in these patients, both in its initial and long-term administration. During the hospital period complete relief of the painful symptoms was achieved in 4 patients; in another the anginal attacks became remarkably less frequent and severe. During the long-term treatment there was one death, which probably was not causally related to the therapy with beta-blocker. In the other patients the follow-up revealed highly satisfactory results.

The assessment of therapy in angina pectoris must be done with utmost caution. Placebo therapy itself has, in fact, been successful in a high proportion of patients (Beecher, 1955). It must also be remembered that propranolol in very large doses has a potent local anaesthetic effect (Morales-Aguilera and Vaughan Williams, 1965). These possibilities seem to be extremely unlikely in our patients for the following reasons: (a) the improvement was obviously dose dependent; (b) after adequate doses of propranolol, parallel with the relief of subjective symptoms, a complete disappearance of the electrocardiographic and of the associated circulatory abnormalities was seen; (c) not only did the episodes of ST segment elevation accompanied by pain cease after treatment, but, and this seems convincing, the episodes that previously occurred and were unnoticed by the patients also ceased. It is useful to remember that the former and the latter were in almost equal proportions before beta-blockade. This first conclusion seems, therefore, feasible: propranolol, administered continuously and in adequate doses, was remarkably effective in preventing attacks of Prinzmetal's variant form of angina.

The attacks were not secondary to circulatory changes which acutely increase work or oxygen consumption of the heart. No pattern could be established for the success of the drug as regards the changes induced in the basal blood pressure, left ventricular work, and tension time index. On the basis of these facts, the mechanism of propranolol in preventing the anginal attacks in question is hard

to interpret. A temporary increased tonus of a large atherosclerotic coronary artery with a narrow lumen was suggested by Prinzmetal *et al.* (1959) as the cause of attacks of pain in this form of angina. Though our haemodynamic observations do not provide crucial evidence in favour of this hypothesis, however, they do not contrast with the possibility of a sudden and important reduction in the myocardial blood supply associated with episodes of electrocardiographic abnormalities. On the basis of Prinzmetal's suggestion one should infer a direct or mediated influence of the propranolol on coronary vasomotility.

The pattern of measured circulatory parameters which are more closely related to myocardial contractility (namely, isovolumic contraction time, and mean rates of isovolumic pressure development and systolic ejection) shows an obvious improvement of the latter after propranolol administration. In addition, in the patient whose anginal episodes were not completely abolished, cardiac function was improved. If it is true that in the two patients with recent myocardial infarction a better cardiac performance could merely be due to the natural process of healing of the lesion, in the other three subjects little doubt exists about the favourable influence of the drug. In the patients investigated, therefore, propranolol administration was not only effective in preventing the episodes of acute heart failure associated with the anginal attacks, but also obviously improved the basal cardiac function. The latter observation certainly contrasts with those of many authors (Hamer and Sowton, 1965; Epstein *et al.*, 1965; Sonnenblick *et al.*, 1965; Murray *et al.*, 1966; Nakano and Kusakari, 1966; Robin *et al.*, 1967; Parker, West, and Di Giorgi, 1968; Wolfson and Gorlin, 1969). In this respect, it must be emphasized that the effects of propranolol on cardiac function were evaluated in our patients after long-term administration of the drug and also after the anginal attacks had completely or almost completely disappeared. If an improved blood supply to the heart were the true mechanism by which propranolol prevents the attacks of the variant form of angina, the finding of a better cardiac function could reasonably be explained.

In this, as in other forms of angina pectoris (Amsterdam *et al.*, 1969), the successful use of propranolol seems strictly related to adequate and individual dosage. In the absence of untoward effects, the dose of propranolol should be increased until the optimal effect on anginal pain is achieved. There is suggestive evidence that the wide variation in the effective dose of propranolol may be due to

differences in enteric absorption (Grant *et al.*, 1966).

Of considerable importance is the almost complete absence of side effects. Because of its efficacy and safety, propranolol therapy seems indicated in patients with Prinzmetal's angina pectoris.

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