PAPERS AND ORIGINALS

Effect of New β-Adrenergic Blocking Agent, Atenolol (Tenormin), on Pain Frequency, Trinitrin Consumption, and Exercise Ability

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Summary

In 11 patients with severe angina pectoris a new β-blocking drug, atenolol (Tenormin; I.C.I. 66082), was found in a double-blind randomized trial to reduce significantly the frequency of anginal attacks ($P < 0.001$) and the amount of trinitrin consumed ($P < 0.03$) in comparison with practolol and placebo. There was no significant improvement in the patients' ability to exercise on the bicycle ergometer.

Introduction

β-Blocking drugs have an established place in the treatment of angina.[1] Though propanolol, oxprenolol, and practolol are all effective[2-4] no single drug has been successful in all anginal patients. The new β-blocker—atenolol (Tenormin; I.C.I. 66082), 4-(2-hydroxy-3-isopropylaminopropoxy)-phenyl acetamide—has been shown in animal experiments to possess a combination of pharmacological properties not possessed by any other β-adrenergic blocker. It is a potent specific inhibitor of cardiac β-receptors. It is cardioselective but lacks both membrane stabilizing and intrinsic sympathomimetic activity.[5] These properties led us to believe that it may be a useful drug in the management of patients with angina pectoris.

We report here on a comparison of the effects of orally administered I.C.I. 66082, practolol, and placebo on patients with established angina pectoris. We compared their symptomatic response, consumption of glyceryl trinitrate, and their ability to exercise on the bicycle ergometer while taking the three drugs in varying doses in a randomized double-blind fashion.

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Patients and Methods

Eleven men, with an average age of 56 years, took part in the trial. All were being seen regularly by one of us in the outpatient clinic, and all had had typical angina pectoris for more than six months which was not crescendo in nature, was precipitated by exertion, and was rapidly relieved by rest or glyceryl trinitrate. During exercise testing all patients developed typical angina; eight had S-T segment depression of 1·0 mV or more. The three patients with typical angina and no S-T depression were among those who had proved significant coronary artery disease on selective angiography.

Six patients had normal electrocardiograms at rest and three had ST-T wave changes only. Two patients had evidence of previous myocardial infarction which had been stable at least six months before the trial. Nine of the 11 patients had had selective coronary angiograms showing significant coronary artery disease.

All 11 patients were taking β-blockers as they entered the trial. Glyceryl trinitrate was the only other drug being taken by any of the patients except for two patients who had been taking clofibrate (Atromid-S 500) for several years.

TRIAL DESIGN

Each patient was seen every two weeks for 12 visits. All visits were at the same time of day for each patient and were held in the same centrally heated room. All patients had previous experience with the bicycle ergometer (Elema Schonander) in the same room.

Run-in Period.—Before the trial started the patients were tested on the ergometer while on no medication and then at two two-weekly intervals while on placebo. This was felt to be a satisfactory "run-in" period and also established a reproducible endpoint for angina in each patient.

Patient Assessment.—At each visit the patients were examined and an electrocardiogram recorded; pulse and blood pressure were recorded at rest while sitting on the bicycle. A 20-ml sample of venous blood was taken for estimation of haemoglobin, white cell count, erythrocyte sedimentation rate, electrolytes, blood urea, liver function, and plasma level of the drug being taken for the previous fortnight. Exercise on the bicycle ergometer in the upright position, with electrocardiograph monitoring leads V5 and V6 attached, was performed for three minutes at 200 k.p.m. At the end of each 3-minute period the load was increased by 200 k.p.m. without pause for rest. The test was stopped when the patient developed typical anginal chest pain.

Drug Administration.—Oral practolol, placebo, and I.C.I. 66082 were given in the following doses, each dose being for one two-week period: I.C.I. 66082, 50 mg, 100 mg, and 200 mg; practolol 100 mg, 200 mg, and 400 mg; placebo 50 mg, 100 mg, and 200 mg. All these doses were given twice a day. The drugs were administered by the pharmacist in a double-blind randomized fashion without the knowledge of the supervising physician. All tablets looked alike and at each visit remaining tablets were counted by the pharmacist. The number of glyceryl trinitrin tablets consumed was also counted and checked against the patients' recorded consumption. Between visits the patient recorded the daily number of anginal attacks during normal activities and the number of glyceryl trinitrate tablets consumed.

Results

Patients.—Fifteen patients were originally accepted for the trial. Two patients were withdrawn after several weeks of the trial because of unreliability. A third patient died suddenly on the first day of the run-in period. Historically he had suffered an acute myocardial infarction. Another patient complained of tiredness and weakness during the eighth two-weekly period and was found to have a sinus bradycardia of 38/min. He was taking I.C.I. 66082 in a dose of 100 mg twice a day. The electrocardiogram showed frequent ventricular ectopic beats which persisted after withdrawal of the drug and it was presumed that progression of the underlying disease was the most likely cause for the bradycardia and ventricular ectopics. Side effects on all three drugs were uncommon. Fatigue was less common than expected and may have been related to the fact that all of the patients had had previous experience with β-blockers.

Effect of I.C.I. 66082 on Anginal Attacks and Trinitrin Consumption.—The average number of anginal attacks and trinitrin tablets consumed by each patient while taking placebo and each dose of the two active drugs is shown in table I. The number of attacks and trinitrin tablets consumed were averaged overall for the periods in which placebo was taken. When taking I.C.I. 66082 all patients had significantly fewer attacks of angina ($P<0.001$) and consumed significantly fewer trinitrin tablets ($P<0.03$).

TABLE I—*Average Number of Anginal Attacks and Trinitrin Tablets Consumed and Total Work Performed on Bicycle Ergometer*

Drug	Placebo	I.C.I. 66082 (mg b.i.d.)			Practolol (mg b.i.d.)		
		50	100	200	100	200	400
No. of attacks of angina	20·78	8·47	9·21	7·64	13·71	13·10	13·76
No. of trinitrin tablets consumed	11·42	6·29	8·16	4·15	9·72	9·54	9·64
Exercise performed (k.p.m.)	2535	2792	2679	2991	2708	2445	2661

Effect of I.C.I. 66082 on Total Exercise Performed.—To investigate sequence effects the placebo periods were extracted and compared. During the run-in period all patients were on placebo, and during the trial up to four patients were on placebo at any given visit. Analysis of variance was carried out, fitting patients and visit in the model, and it was found that while on placebo there were no significant differences between visits for any variable except k.p.m. ($P>0.1$ for all variables except k.p.m., for which $P<0.06$). When the run-in period was removed, however, there was no evidence of sequence effects for k.p.m. either ($P>0.03$). Thus any differences in exercise performed were not due to the effects of training. The maximum average amount of work was performed when the patients were taking I.C.I. 66082 200 mg twice a day (table I). The mean increase in total work performed while on I.C.I. 66082 was 13% (range 10-18%) and on practolol the mean increase was 5% (range 5-7%). The increases were not statistically significant.

TABLE II—*Pulse and Blood Pressure before and after Exercise*

	Pulse		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)	
	Before	After	Before	After	Before	After
Placebo	82	124	131	159	86	84
Practolol (mg b.i.d.):						
100	76	112	123	148	82	84
200	81	105	126	155	86	82
400	73	103	119	140	80	80
I.C.I. 66082 (mg b.i.d.):						
50	64	101	121	135	76	80
100	58	97	119	135	79	77
200	62	92	118	140	77	80
I.C.I. 66082 *v.* placebo (P)	<0·001	<0·001	<0·06	<0·001	<0·002	N.S.

Effect of I.C.I. 66082 on Pulse Rate and Blood Pressure.—The average pulse rate, and systolic and diastolic blood pressure at rest and immediately after exercise are shown in table II. There were significant differences in all three variables at rest when patients were taking I.C.I. 66082 compared with placebo. After exercise there were significant differences in pulse and systolic blood pressure but not in diastolic blood pressure.

Discussion

The pharmacological properties of I.C.I. 66082 are summarized and compared with those of other β-adrenergic blocking drugs in table III. I.C.I. 66082 is a unique β-adrenergic blocker. Its cardioselectivity frees it from the limitation placed on non-selective β-blockers that they cannot be given to patients with asthma or chronic obstructive airways disease without the risk of intensifying bronchospasm. Astrom and Vallin[6] have shown that I.C.I. 66082 in a single intravenous dose, in contrast to propranolol,[7] did not increase airways resistance.

Though practolol shares with I.C.I. 66082 cardioselectivity it also possesses intrinsic sympathomimetic activity, which on theoretical grounds could be considered disadvantageous in not producing either optimal hypotensive effect in hypertensive patients or optimal relief of angina. Some clinical trials suggest that practolol is not as effective as propranolol in the relief of angina[8] though others[9] do not show any significant difference between the two drugs. In our patients practolol was less effective than I.C.I. 66082 in terms of reducing frequency of anginal attacks, trinitrin consumption, and pulse and blood pressure.

TABLE III—*Pharmacological properties of I.C.I. 66082 and Other β-Blockers*

Drug	β-Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity	Cardioselectivity
Propranolol	+	+	−	−
Oxprenolol	+	+	+	−
Practolol	+	−	+	+
I.C.I. 66082	+	−	−	+

Like practolol I.C.I. 66082 reduces cardiac output both at rest and during work. This effect is due to a decrease in heart rate; stroke volume is unchanged.[6] Propranolol also reduces stroke volume, an effect which may be due to depression of myocardial function as well as blockade of the peripheral

circulation.[10] I.C.I. 66082 would therefore be a more appropriate β-blocker to use in those at risk of developing cardiac failure. In our patients there was no evidence of cardiac failure while on I.C.I. 66082. I.C.I. 66082 has two other theoretical advantages: it lacks membrane stabilizing activity, which in extremely high doses is thought to delay cardiac conduction, and it has been shown in animals that I.C.I. 66082 does not cross the blood brain barrier (I.C.I. introductory animal experiments) and is therefore less likely to cause the troublesome dreams reported with some other β-blockers.[11]

In our highly selected group of patients, each of whom acted as his own control, I.C.I. 66082 was found to be superior to practolol and placebo in all values assessed. The number of anginal pains and amount of trinitrin consumed in patients on I.C.I. 66082 was significantly reduced ($P<0.001$ and $P<0.03$ respectively).

The improved ability to exercise on the bicycle ergometer while taking I.C.I. 66082 was not as great as perhaps expected from the reduction in trinitrin intake. It was not uncommon to find that a patient expressed a feeling of wellbeing and a reduced incidence of anginal pains during a particular two-weekly period and yet showed no dramatic change in his work performance on the bicycle ergometer.

Each patient took I.C.I. 66082 for a total of six weeks, and during this time no side effects were noted. Skin and eye changes were especially looked for. Haematological and biochemical values remained normal.

We therefore conclude that I.C.I. 66082 in a selected group of patients with severe angina pectoris significantly reduced the frequency of anginal attacks and the need to take trinitrin tablets. It was effective in the convenient dosage of 50 mg twice a day (one tablet twice daily).

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Arterial Occlusion after Cannulation

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Summary

The occurrence of ischaemic changes, arterial occlusion, and other complications which may follow percutaneous arterial cannulation was assessed in a survey of 155 patients. No patient complained of or had signs of ischaemic damage though signs of arterial occlusion were found in 33 patients (22%). These signs were significantly more common after periods of cannulation greater than six hours (43%) than after less than six hours cannulation (17%). During recovery from occlusion all patients had palpable pulsation over the artery even though blood flow seemed to be absent. By the end of follow-up blood flow had returned in 19 of the 33 occluded arteries.

Introduction

Percutaneous arterial cannulation has been performed increasingly often over the last few years, both for continuous direct measurement of the arterial blood pressure and to facilitate repeated blood gas analysis, in spite of the danger of producing ischaemic changes in the limb distal to the cannulation site. Reports of permanent damage such as ischaemia of fingers or muscle wasting near the puncture site seem rare, and a review of 16 studies which included 4566 patients found that the incidence of such severe complications was 0·3%.[1] Occlusion of the artery, however, has resulted from cannulation in many patients without producing subjective or objective signs of ischaemia.[2 3]

We undertook a prospective study to assess the incidence of arterial occlusion and ischaemic changes in patients cannulated by members of the Nuffield Department of Anaesthetics and the relative importance of some of the factors involved in the development of these complications.

Method

A form was completed at the time of cannulation to provide information about the patient and the cannulation procedure.

Post-cannulation observations were all made by one anaesthetist who interviewed patients on the first, third, and seventh days after removal of the cannula. In patients with arterial occlusion more frequent observations were made over a longer period. At each interview the cannulation site and the limb in which it was situated were carefully examined and symptoms referable to the area were asked for. A note was made of the presence of haematoma (bleeding into the tissues with consequent swelling) at the cannulation site, bruising of the skin, and oedema in the limb. Infection was judged to be present when pain, erythema, and oedema were present at the cannulation site.

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