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An eighteen months' study of the clinical response to metoprolol*, a selective β_1-receptor blocking agent, in patients with angina pectoris

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Summary

Following an initial dose response study, metoprolol, a selective β_1-receptor blocking agent, was compared with equipotent dosages of propranolol in a double blind cross-over study, including exercise tolerance tests, on fourteen patients with angina pectoris. Long term therapy with metoprolol then followed until the seventy-second week.

Patients performed 8% more total work on metoprolol with 15% more work recorded up to the onset of S-T depression, in comparison with propranolol. In the long term, there was no significant difference in work performed when the daily dosage of metoprolol was changed from a q.i.d. to a b.d. regime. Metoprolol was shown to be an effective anti-anginal compound with good tolerance and safety, with gradual improvement in underlying myocardial ischaemia during long term treatment.

DURING the last 2 years, there has been increasing clinical interest in the response of angina patients to a new generation of adrenergic β-receptor blocking agents shown to have selectivity towards β_1-receptors. It had been suggested that such compounds might produce therapeutically desirable cardiac β-blockade without the adverse effects associated with constriction of vascular and bronchial smooth muscle resulting from interference with the β_1-receptors.

Practolol was the first to be used extensively in clinical practice, but in view of the increasing adverse reports of oculomucocutaneous syndrome (Felix, Ive and Dahl, 1974; Wright, 1975), and sclerosing peritonitis (Windsor, Kurrein and Dyer, 1975), practolol should now be considered unsuitable as a therapeutic agent in the long term treatment of angina.

Metoprolol (1-(4-(2-methoxyethyl)phenoxy)-3-isopropylamino-propanol) has been described, in animal studies, as a selective antagonist in that it blocked the effects of isoprenaline on the adrenergic β-receptors in the heart in much lower doses than were required to block the effects of isoprenaline on the β-receptors in vascular and bronchial smooth muscle (Ablad, Carlsson and Ek, 1973). Clinico-pharmacologically, it has been shown to be equally selective as practolol when the response to isoprenaline was measured in patients with chronic obstructive lung disease (Thiringer and Svedmyr, 1976). Although the plasma half-life in man is of the order of 3–4 hr, the time for 50% reduction of the maximum pharmacological effect of 100 mg orally on the reduction of exercise tachycardia is 8 hr (Regardh *et al.*, 1975). It is devoid of intrinsic activity and, to date, no metabolites with β-blocking properties have been identified.

It was the aim of this study to investigate during a 9- to 18-month period, the anti-anginal effect, tolerance and safety of metoprolol when given orally to a selected group of patients with steady state angina of at least 3 months' duration, and compare the anti-anginal effects of metoprolol with propranolol in a double-blind cross-over study.

Material and methods

Fourteen patients (twelve male and two female) were selected from out-patients attending the Cardiac Clinic for investigation or review during 1973. The diagnosis of angina pectoris was based on a clinical history of pain, ache or pressure in the chest on physical exertion, relieved by decreasing activity and/or taking nitroglycerin sublingually, together with electrocardiographic evidence of S-T depression during an exercise tolerance test on at least two separate occasions. The patients were aged between 44 and 71 years. Before inclusion in this study, all patients were clinically stabilized on propranolol therapy and were well documented in terms of the response to exercise tolerance, radiological investigation, electrocardiography and laboratory controls. Informed consent was obtained in all cases. A summary of clinical information is presented in Table 1.

In view of the increasing difficulty in hospital

* Metoprolol = H93/26 = CGP 2175.

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TABLE 1. Summary of clinical information

	Sex	Age	Duration of angina in months	Weekly attack rate before study	Trinitrin taken	Previous medical history	ECG	Chest X-ray	Additional therapy
1	M	62	24	3–4	Yes	Pneumonia 1963	Left ventricular strain	Normal	
2	M	63	17	5–7	Yes	Myocardial infarction 1972	Inverted T wave in VI to V IV	Normal	Valium
3	M	71	12	3–4	No	Nil	Left ventricular strain	Normal	
4	F	44	4	3–4	No	Nil	Normal	Normal	Valium
5	M	68	5	3–4	Yes	Nil	Normal	Normal	Hygroton
6	M	65	4	3–4	Yes	Paget's disease left leg 1944	Inverted T wave in III	Normal	Navidrex K Digitalis
7	M	65	17	3–4	Yes	Pneumonia 1924	Depressed ST in V III to V VI	Enlarged heart	
8	M	60	31	3–4	Yes	Myocardial infarction 1971	Left ventricular strain	Enlarged heart	
9	F	54	5	5–7	Yes	Subarachnoid haemorrhage 1964	Depressed ST in I and II & VI to V VI	Normal	Valium
10	M	54	52	3–4	Yes	Myocardial infarction 1969	QT in II III V & V VI	Normal	Aprinox Slow K
11	M	56	40	3–4	Yes	'Dyspnoea' whilst in the army	Depressed RT in III	Normal	Valium
12	M	48	15	3–4	Yes	Duodenal ulcer	Inverted T wave in AVL	Normal	
13	M	50	18	3–4	Yes	Myocardial infarction 1973	QT in III	Normal	
14	M	49	15	3–4	Yes	Myocardial infarction 1974	Q wave in II and III	Normal	

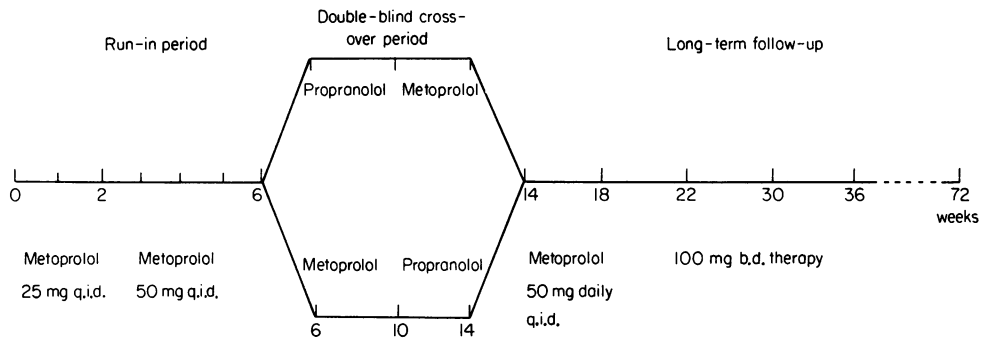

FIG. 1. Design of study.

practice to find patients with 'steady state' angina who would be suitable for a long-term study, considerable time was spent in screening out-patients attending the Cardiac Clinic during a 12-month period. More than 100 patients underwent repeated exercise tolerance tests as part of the routine assessment of their angina state. Although a larger patient sample would have made the interpretation of the results easier, only fourteen were ultimately able to take part and complete the programme.

The design of the study is outlined in Fig. 1. At the commencement of the study there was a run-in period during which previous therapy with propranolol was switched to metoprolol 25 mg at the same daily frequency (q.i.d. in all patients except 5 and 10 who were t.i.d. schedule) for 2 weeks, when a clinical examination and exercise test were performed, and the serum level of metoprolol estimated. For the next 4 weeks, the dose of metoprolol was increased to match the original propranolol therapy on the basis that 40 mg propranolol was equivalent to 50 mg metoprolol relative to the reduction of exercise tachycardia (Johnsson, Nyberg and Solvell, 1975). Clinical examination, exercise test and serum estimations were again carried out, the latter analysis always being carried out on a post-exercise blood sample.

From the sixth to the fourteenth week, there followed a double-blind cross-over period during which the patient received a 4-week course of metoprolol and propranolol at the same dose levels used during the latter part of the run-in period. Clinical examination and an exercise test were carried out at the end of each period with, once again, post-exercise

blood samples being taken for estimation of the plasma level of metoprolol or propranolol, about 10–15 min after the cessation of the exercise test. Drug level estimations were estimated according to the method described by Ervik (1975).

In the subsequent long term follow-up with metoprolol, all patients continued on a dose of at least 50 mg q.i.d. during the first 4 weeks after which the daily dosage was changed to a morning and evening schedule, with the total daily dose remaining unaltered (always provided there was no deterioration of the anginal stages throughout the study). The exercise test was performed at the same time and usually 2–3 hr after the morning dose of tablets.

Full laboratory control including determination of haemoglobin, white cell count, urinalysis, liver function tests, electrolytes and blood urea, and lipid levels, were carried out at each 4-week visit during the first 14 weeks of the study, and thereafter every 8 weeks.

The exercise test was performed on an electrically braked Elema-Schonander bicycle ergometer using three 3-min step-wise periods, starting in most cases at a load of 50 W, and increasing to 75 W, and possibly 100 W. ECG recordings were made during the last 15 sec of each phase of exercise, and during the post-exercise period from a modified left praecordial lead with the reference electrode to the left leg being sited on the forehead, and the right leg to the right arm, to avoid motion and positional artefacts. The diagnostic criterion of ischaemic electrocardiographic change was the development of at least 1 mm depression of the S-T segment present in five successive beats with a stable isoelectric baseline.

Ratings of leg fatigue, dyspnoea and perceived exertion were assessed on completion of each exercise test based on the following scales: 1, nil; 2, slight; 3, moderate; 4, extreme.

No diaries of the attack or trinitrin (TNT) consumption were kept during the study, as previous attempts to do so were considered unreliable in patients with such relatively infrequent attacks. At each visit, full documentation was recorded on special patient forms provided, including a note of the incidence and severity of unwanted effects (i.e. side effects). An X-ray of the chest was taken before the commencement of the study and again during the fourth month in order to record the cardiac size and shape, and the possible presence of pulmonary congestion. Throughout the study, previous treatment with other drugs, e.g. TNT, valium, diuretic, digitalis, continued unchanged.

Statistical method

Statistical significance was analysed by Wilcoxon's matched pairs signed ranks test for comparison of paired data.

Results

Thirteen of the patients have subjectively remained stable in terms of their attack rate and TNT consumption throughout the period under study (November 1973 to April 1975). Patient 11 developed an acute chest infection in November 1974 and was withdrawn from the trial. At this stage, he had been on 200 mg metoprolol daily for 36 weeks.

Run-in period

The means of the exercise tolerance levels at the sixth week showed little variation compared to the pre-trial values (when on propranolol) although, as seen in Table 2, there was a reduction on the low dose of metoprolol of 25 mg q.i.d. during the initial 2 weeks ($P < 0.02$). Means of the resting heart rate values were 61·5/min at the second week, falling to 56·7/min at the fourth week.

TABLE 2. Exercise tolerance (expressed in W min) in patients before and during run-in period

	Propranolol 40 mg q.i.d.	Metoprolol 25 mg q.i.d.	Metoprolol 50 mg q.i.d.
Patient	Pre-trial	2nd week	6th week
1	800	600	600
2	675	375	490
3	525	565	600
4	775	775	775
5	450	375	450
6	415	250	225
7	340	375	510
8	525	475	575
9	300	360	340
10	500	625	660
11	275	350	315
12	575	575	675
13	665	550	600
14	475	475	525
Means	521·1	480·4	524·3
		$P < 0.02$	

Cross-over period

(a) Total work. There was a statistically significant increase ($P < 0.04$) in the total work performed during the metoprolol period in comparison with propranolol (Table 3).

On looking at the individual responses, one patient showed a better response to propranolol and four patients a better response to metoprolol, based on a 20% difference in the exercise tolerance results.

(b) ECG reaction. More work was recorded up to the onset of S-T depression with metoprolol than propranolol ($P < 0.02$). There were two patients who did not have evidence of S-T depression when on metoprolol, which was regarded as of no clinical significance as they both performed comparable degrees of work on the two compounds.

(c) Heart rate and blood pressure recordings. These were the same in the two groups, both at rest and at the end of exercise, indicating equipotency of the dose ratio accepted for the study (Table 3).

(d) Ratings of leg fatigue, dyspnoea and perceived exertion. These remained the same in the two groups.

TABLE 3. Means of the daily dose, plasma levels, exercise tolerance limits, heart rates and systolic blood pressure before and after exercise, at the end of 4 weeks' treatment with metoprolol and propranolol (DBXO study)

	Metoprolol	Propranolol	*P* values
Daily dose in mg	178·5	142·8	
Plasma level ng/g plasma	61·6	59·8	
Exercise tolerance (W min)	556·7	513·5	
s.e. mean	49·3	43·3	0·04
Exercise tolerance to onset of pain	422·5	441·5	N.S.
Exercise tolerance to 1 mm ST depression	458·3	397·1	
	458·3	397·1	
s.e. mean	55·6	47·9	0·02
Resting heart rate	57·8	57·3	
s.e. mean	1·5	1·7	N.S.
Heart rate at end of exercise	97·1	96·3	
s.e. mean	3·5	4·5	N.S.
Resting systolic pressure	111·8	114·3	
s.e. mean	3·9	3·6	N.S.
Systolic pressure at end of exercise	157·1	152·5	
s.e. mean	4·9	5·8	N.S.

TABLE 4. Stratification of data from the DBXO study—means of results from fourteen patients—exercise tolerance expressed in W min

		Metoprolol	Propranolol
< 60 years old	(7)	587	532
> 60 years old	(7)	526	495
No past history of myocardial infarction	(9)	509	493
Past history of myocardial infarction	(5)	642	550

Subjectively the anginal attack rate remained unchanged during the two periods of treatment.

(e) Plasma levels. Variable levels were noted in the fourteen patients during this cross-over period, with a range of 14–121 ng/g plasma (mean, 61·6) for metoprolol, and a range of 5–159 ng/g plasma (mean 59·8) for propranolol. The therapeutic plasma level for both drugs was of the order of 50–100 ng/g plasma in the method used.

(f) Although the numbers are limited, stratification of the data from the cross-over study suggested that those patients with a previous history of a myocardial infarction had a better exercise tolerance when on either metoprolol or propranolol, in comparison to those patients with no such past history (Table 4).

Long-term follow-up

Means of the exercise tolerance tests from the eighteenth to the seventy-second week of the study, showed little variation throughout this period, although there was a suggestion of a gradual decrease in the extent of S-T depression recorded at the end of exercise (Table 5). There was no significant difference in the exercise tolerance limits as a result of doubling the morning dose when changing from a q.i.d. to a b.d. regime after the eighteenth week (Table 5). At the seventy-second week, five of ten patients were taking 100 mg b.d.

Means of the plasma levels of metoprolol during this same period showed little varation (Table 6), in contrast to a dose–response result noted at the second and sixth week of the study.

In regard to the laboratory control, there was no significant change in haemoglobin levels, blood counts or liver function tests. All urine analyses and serum electrolyte levels remained within normal limits throughout the period under study.

Side effects were infrequent and only the following were considered of interest. Lassitude in association with excess dreams at night, occurred in a patient when the dose of metoprolol was increased from 150 mg to 200 mg daily, but disappeared when the dose was reduced 10 days later. Bradycardia (heart rate

TABLE 5. Means of the exercise tolerance (expressed in W min), work performed up to 1mm ST depression, and ST depression at the end of exercise in angina patients during treatment with metoprolol up to the seventy-second week (n=14 up to the thirtieth week; thereafter n=10)

	Pre-trial	Eighteenth week	Twenty-second week	Thirtieth week	Forty-second week	Fifty-fourth week	Seventy-second week
Exercise tolerance	521	506	496	515	492	493	471
Work up to 1 mm ST depression	375	428	400	448	439	420	454
ST depression at end of exercise in mm	1·3	1·3	1·3	1·5	1·2	1·0	0·8

Note: b.d. therapy initiated after the eighteenth week.

TABLE 6. Means of the serum levels of metoprolol (expressed in ng/g plasma) in angina patients (n=11) up to the seventy-second week of the study

	Second week 25 mg q.i.d.	Sixth week 50 mg q.i.d.	Eighteenth week 50 mg q.i.d.	Twenty-second week 100 mg b.d.	Fifty-second week 100 mg b.d.	Seventy-second week 100 mg b.d.
	22·9	55·6	111·3	121·1	108·4	120·5
Range	5–54	12–136	50–245	58–182	36–247	51–256

42 beats/min) was observed in another patient during the fourth month of treatment when the dose was increased to 200 mg daily. Although the patient was asymptomatic, the dose was reduced to 100 mg daily and the resting heart rate rose to 54 beats/min. One patient complained of heartburn when the dose of metoprolol was changed from 50 mg q.i.d. to 100 mg b.d. This disappeared on reverting to the original dose schedule.

Discussion

There are, at present, five known β-blockers which are said to be cardio-selective, of which practolol (Dunlop and Shanks, 1968) was the first to be developed. While the differing pharmacological profiles of this group are interesting, there are few published reports of comparative clinical studies in angina. Jackson, Atkinson and Oram (1975) have recently compared tolamolol, propranolol, practolol and placebo given during five 1-monthly treatment periods, and concluded that tolamolol was equal in anti-anginal efficiency to propranolol, and superior to practolol. In an acute, oral study, metoprolol, alprenolol (non-selective) and H87/07 (cardio-selective), have all been shown to have a similar effect on exercise-induced angina pectoris (Adolfsson *et al.*, 1974). In the present study, a definite dose response relationship was seen in those ten patients who received the higher dose of 200 mg daily, the effect of which assumes the order of about a 20% increase in total work at the eighteenth week in comparison with the second week results when 100 mg daily was given.

In the cross-over study, exercise tolerance was 8% higher after metoprolol than after propranolol, a finding very similar to that reported by Astrom and Vallin (1974) in a comparison of ICI 66082 and propranolol. Taking a 20% difference in the degree of exercise tolerance, one patient showed a better response to propranolol, and four patients a greater improvement with metoprolol. There was little variation in the systolic blood pressure levels recorded, and post-exercise delta heart rates were similar except in one patient. This confirmed the equipotency of the doses used.

Although stratification of the data suggested a better exercise tolerance by those patients with a previous history of myocardial infarction when on either metoprolol or propranolol, the results were not statistically significant. Similar findings have, however, been previously reported (Hetherington *et al.*, 1973).

During the long-term follow-up, the degree of exercise tolerance remained unchanged in those patients whose dosage regime was altered from q.i.d. to b.d. (Table 5). Subjectively, their anginal state remained stable and unaltered, and it would therefore appear that a dosage regime of metoprolol 100 mg b.d. was acceptable. These findings are in accordance with the pharmacodynamic studies in man (Johnsson, Regardh and Solvell, 1975).

Since the association between S-T segment depression and the presence of myocardial ischaemia was first discovered (Feil and Segal, 1928), there have been many conflicting claims and conclusions regarding the results of exercise testing in patients being assessed for the presence of coronary artery disease (Redwood and Epstein, 1972). The more recent confirmation of the production of lactate (a biochemical index of ischaemia) at the onset of S–T segment depression during exercise by patients with known coronary artery disease (Boudoulas *et al.*, 1974), should add support to the acceptance of 1 mm of S–T segment depression on exercise testing as evidence of ischaemic heart disease (Hartley, 1975). Myocardial ischaemia occurs when myocardial oxygen consumption exceeds the capacities of the coronary arteries to deliver oxygen. Propranolol has been shown to reduce S–T segment elevation occurring during coronary occlusion in the dog, suggesting that sympathetic blockade in reducing myocardial contractility may also have reduced oxygen requirements (Braunwald *et al.*, 1969). Similar findings in man have been observed following intravenous potassium-glucose-insulin treatment in cases of acute myocardial infarction (Sodi-Pallares *et al.*, 1962), and also in angina patients who were paced before and after aorto-coronary bypass surgery (Chatterjee *et al.*, 1975). Although still not universally accepted as definite evidence of myocardial ischaemia, S–T segment depression is now being used more frequently in the strict clinical evaluation of patients' progress (Bruce, 1974; Chatterjee *et al.*, 1975). During the 72 weeks of the present study, there was a steady decrease in the extent of S–T depression at the end of exercise, as well as a gradual

increase of up to 20% in total work performed up to the onset of 1 mm S–T depression, suggesting a gradual improvement in underlying myocardial ischaemia during long term treatment. While the amount of exercise required to elicit S-T segment depression is said to be closely related to the extent of coronary artery obstructive disease (Kattus, 1974) as demonstrated in coronary angiograms, it is difficult to envisage any change occurring in these major branches during several months of treatment. The interpretation of the continuous improvement in S–T changes throughout the study may well be impossible until there is a reasonable method of assessing the development of a collateral circulation in the myocardium.

The increasing number of adverse reports with practolol has focused closer attention on the possibility of adverse reactions to long term treatment with the newer β-blocking drugs. In this study, there were no cases of oculomucocutaneous syndrome, nor of sclerosing peritonitis. Assessment of antinuclear factor after 15 months' treatment showed no significant abnormality.

Metoprolol has been shown in this 18-month study to be an effective anti-anginal compound with good tolerance and safety. Its effect on exercise tolerance in comparison with propranolol may well be related to its β_1-receptor selectivity.

References

ABLAD, B., CARLSSON, E. & EK, L. (1973) Pharmacological studies of two new cardio-selective adrenergic beta-receptor antagonists. *Life Sciences*, **12**, 107.

ADOLFSSON, L., ARESKOG, N., FURBERG, C. & JOHNSSON, G. (1974) Effects of single doses of alprenolol and two cardioselective beta-blockers (H87/07 and H93/26) on exercise-induced angina pectoris. *European Journal of Clinical Pharmacology*, **7**, 111.

ASTROM, H. & VALLIN, H. (1974) Effect of a new beta-adrenergic blocking agent, ICI 66082, on exercise haemodynamics and airways resistance in angina pectoris. *British Heart Journal*, **36**, 1194.

BOUDOULAS, H., COBB, T.C., LEIGHTON, R.F. & WILT, S. (1974) Myocardial lactate production in patients with angina-like chest pain and angiographically normal coronary arteries. *American Journal of Cardiology*, **34**, 501.

BRAUNWALD, E., COVELL, J.W., MAROKO, P.R. & ROSS, J. (1969) Effect of drugs and of counter pulsation on myocardial oxygen consumption. Observations on the ischaemic heart. *Circulation*, **39/40** (Suppl. 4), 220.

BRUCE, R.A. (1974) Progress in exercise cardiology. In: *Progress in Cardiology* (Ed. by Paul N. Yu & John F. Goodwin), vol. 3, p. 146.

CHATTERJEE, K., MATLOFF, J.M., SWAN, H.J.C., GANZ, W., SUSTAITA, H., MAGNUSSON, P., BUCKBINDER, N., HENIS, M. & FORRESTER, J.S. (1975) Improved angina threshold and coronary reserve following direct myocardial revascularization. *Circulation*, **51/52** (Suppl. 1), 166.

DUNLOP, D. & SHANKS, R.G. (1968) Selective blockade of adrenoceptive beta-receptors in the heart. *British Journal of Pharmacology and Chemotherapy*, **32**, 201.

ERVIK, M. (1975) Quantitative determination of metoprolol in plasma and urine by gas chromatography. *Acta pharmacologica et toxicologica*, **36** (Suppl. V), 136.

FEIL, H. & SIEGEL, M.L. (1928) Electrocardiographic changes during attacks of angina. *American Journal of Medical Science*, **175**, 255.

FELIX, R.H., IVE, F.A. & DAHL, M.G.C.(1974) Cutaneous and ocular reactions to practolol. *British Medical Journal*, **4**, 321.

HARTLEY, L.H. (1975) Value of clinical exercise testing. *New England Journal of Medicine*, **293**, 400.

HETHERINGTON, D.J., COMERFORD, M.B., NYBERG, G. & BESTERMAN, E.M.M. (1973) Comparison of two adrenergic beta-receptor blocking agents, alprenolol and propranolol, in the treatment of angina pectoris. *British Heart Journal*, **35**, 320.

JACKSON, G., ATKINSON, L., & ORAM, S. (1975) Double-blind comparison of tolamolol, propranolol, practolol, and placebo in the treatment of angina pectoris. *British Medical Journal*, **1**, 708.

JOHNSSON, G., REGARDH, C. SOLVELL, L. (1975) Combined pharmacokinetic and pharmacodynamic studies in man of the adrenergic beta-one receptor antagonist, metoprolol. *Acta pharmacologica et toxicologica*, **36** (Suppl. V), 31.

JOHNSSON, G., NYBERG, G. & SOLVELL, L. (1975) Influence of metoprolol and propranolol on haemodynamic effects induced by physical work and isoprenaline. *Acta pharmacologica et toxicologica*, **36** (Suppl. V), 69.

KATTUS, A.A. (1974) Exercise electrocardiography: recognition of the ischaemic response, false positive and negative patterns. *American Journal of Cardiology*, **33**, 721.

REDWOOD, D.R. & EPSTEIN, S.E. (1972) Uses and limitations of stress testing in the evaluation of ischaemic heart disease. *Circulation*, **46**, 1115.

REGARDH, C., JOHNSSON, G., DORDO, L. & SOLVELL, L. (1975) Comparative bioavailability and effect studies on metoprolol administered as ordinary and slow-release tablets in single and multiple doses. *Acta pharmacologica et toxicologica*, **36** (Suppl. V), 45.

SODI-PALLARES, D., TESTELLI, M.R., FISHLEDER, B.L., BISTENI, A., MEDRANO, G.A., FRIEDLAND, C. & DE MICHELI, A. (1962) Effects of an intravenous infusion of a potassium–glucose–insulin solution on the electrocardiographic signs of myocardial infarction. *American Journal of Cardiology*, **9**, 166.

THIRINGER, G. & SVEDMYR, N. (1976) Interaction of orally administered metoprolol, practolol and propranolol with isoprenaline in asthmatics. *European Journal of Clinical Pharmacology* (in press).

WINDSOR, W.O., KURREIN, F. & DYER, N.H. (1975) Fibrinous peritonitis: a complication of practolol therapy. *British Medical Journal*, **2**, 68.

WRIGHT, P. (1975) Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *British Medical Journal*, **1**, 595.