Assessment of propranolol in angina pectoris

Clinical dose response curve and effect on electrocardiogram at rest and on exercise

B. N. C. Prichard¹ and P. M. S. Gillam²

From Clinical Pharmacology Section, Medical Unit, University College Hospital Medical School, University Street, London

In a double-blind variable multidose trial of propranolol in angina pectoris, the maximum benefit in terms of reduced anginal pain, reduced trinitrin consumption, reduction in total duration of pain, increase in pain-free days, improvement of ST segment changes associated with ischaemia, and acute exercise tolerance, was obtained with the maximum dose of propranolol (av. dose 417 mg, range 80-1280). Progressively less benefit was seen with half this dose, one-quarter, and one-eighth dose, though even one-eighth dose was significantly superior to placebo. As dosage was increased there was a progressive reduction in pulse rate. In 6 hypertensive patients in the trial blood pressure fell as dose was increased up to half full strength, but there was no further fall on doubling to full dose.

Since early trials demonstrating benefit from propranolol in angina pectoris whether given intravenously (Hamer *et al.*, 1964) or orally (Keelan, 1965; Gillam and Prichard, 1965), there have been numerous confirmatory studies.

The majority of trials showing benefit have in fact used a fixed dosage. Keelan (1965) used a total of 90 mg daily, Ginn and Orgain (1966) used 160 mg daily, Grant *et al.* (1966) 240 mg daily, Rabkin *et al.* (1966) 200 mg daily, Gianelly *et al.* (1967) 160 mg daily, Harley and Davies (1968) 160 mg daily. Wolfson *et al.* (1966) varied the dose of propranolol to suit individual requirements, and used between 160 and 280 mg. In our first study we adjusted the dose to suit the individual patient using between 120 mg and an arbitrary upper limit of 400 mg (Gillam and Prichard, 1965).

In a further variable dose trial again using a maximum dosage of 100 mg q.d.s., in addition to the full dose, half dose and placebo tablets were included (Gillam and Prichard, 1966). Of the 17 patients in this trial, 16 had fewer attacks of angina and consumed less trinitrin on active propranolol than on placebo

($P=0.00028$). Of these 16, 13 had greater benefit on full strength (average dose 304 mg daily) than on half strength (average dose 152 mg daily) ($P=0.02$).

Two other trials have used more than one dose level, but both were basically fixed dose studies as all patients received the same dosages. In one of these trials (Hebb, Godwin, and Gunton, 1968), patients reported no improvement on 40 mg daily, a reduction to an average of 78 per cent of the attacks on placebo on 80 mg daily ($P<0.05$), and on 160 mg daily to 59 per cent of the attacks experienced on placebo tablets ($P<0.001$). Mizgala, Khan, and Davies (1969) in 15 patients observed an average reduction in trinitrin consumption of 48 per cent on 160 mg daily ($P<0.01$), but on doubling the dose the further reduction (12%) was not significant.

In the present study placebo and four dose levels of propranolol, adjusted to the need of each individual patient, were administered to investigate the effect of higher doses of propranolol and to examine further the hypothesis that for maximum benefit in angina the maximum tolerated dose should be given.

Method

Trial design (i) *Run-in period and determination of maximum dosage*

As with our previous trials (Gillam and Prichard, 1965, 1966), patients were seen for at least three

Received 3 September 1970.

¹ Senior Lecturer in Clinical Pharmacology and Therapeutics.

² Present appointment: Consultant Physician, Salisbury General Hospital.

months before the start of the trial. In the present study patients were seen at fortnightly intervals under similar conditions to those in the trial proper, and the dosage was adjusted until the pulse rate was 55–60 after resting on the couch for three minutes. If a patient experienced any side effect before this was achieved dosage was slightly reduced and no further increment was made.

(ii) Administration of tablets

Tablets identical in appearance and taste were prepared containing 40 mg, 20 mg, 10 mg, 5 mg, and no propranolol. Patients swallowed the tablets whole with water. They are very bitter and if kept on the tongue a local anaesthetic effect is apparent which could identify the active preparations. Patients received each of these 5 strengths for 2 weeks in random order. After 10 weeks patients had therefore received each strength once. This 10-week cycle was then repeated twice. There was therefore a total of 30 weeks for the trial. The randomization was made complete each 10 weeks to minimize the influence of long-term fluctuations on the patients' angina and to eliminate the possibility of individual patients receiving all of one-strength of tablets in either summer or winter months.

(iii) Record sheets

Throughout the run-in and trial, patients kept a weekly record sheet; each day being divided into four periods. They were asked to record all their attacks of angina, the time of onset, duration, and to grade the severity as mild, moderate, or severe. They noted the number of trinitrin tablets consumed.

(iv) Clinic routine

Patients were seen by the same physician at each visit, they were asked standard questions about their general condition and angina, their record sheets were checked, and the trinitrin removed from bottles that had been supplied containing a precounted number of tablets. At their visits patients were asked to assess their general impression of their angina over the preceding two weeks and to choose a reply from the question, 'had their angina in the last two weeks been better, same, worse, much better, or much worse?' They were also asked how they felt and asked to choose a reply from ill, fair, well, very ill, or very well. Blood pressure and pulses were taken 1 minute and 3 minutes after lying supine on the couch, 1 minute after standing, and then again after a simple exercise test. This varied from walking up and down an adjacent corridor to ascending and descending stairs, according to the patient's capability. Patients were seen at the same time of day on each occasion. Their weights were recorded.

Patients The patients all had anginal chest pain, precipitated by exercise and relieved by rest and trinitrin, and with electrocardiographic changes of ischaemia. They were otherwise unselected. They

were aware that the study was a trial and their participation was invited. Those patients taking part in the exercise tests signed a form on each occasion indicating that they understood that this was not part of their treatment.

Effect of trinitrin on blood pressure Cases 2, 3, 5, 8, 10, and 13 took part in our previous variable dose level trial (Gillam and Prichard, 1966) where propranolol full strength, half strength, and placebo were given. In this trial they had their blood pressures measured supine and standing after chewing 0.5 mg trinitrin. These results have not been published previously. These patients received an average of 267 mg propranolol a day as their full dose. The actual doses given were the same as in the present trial (see Table 1), except Case 8 who received 280 mg a day.

Acute exercise tests Ten patients attended fortnightly for the first two 10-week cycles of the trial for acute exercise studies, i.e. two exercise tests were performed on each strength. Studies were performed at the same time of the day on each occasion. Patients cycled supine on an ergometer at levels of work from 50–100 watts, according to their capabilities, until the onset of anginal pain. The effect on the most suitable lead of the electrocardiogram was studied; ST changes were assessed without knowledge of the patient or his dosage.

Results

Patients Sixteen patients entered the run-in period of the trial and all completed the trial except Cases 1 and 5 (see Table 1, reasons indicated) who only completed two cycles of treatment (i.e. 4 weeks on each dose level).

Dosage The dosages used as full strength are listed in Table 1. One patient tolerated the arbitrary maximum dosage (Case 6). A pulse rate between 55 and 60 in the supine position was the reason for not increasing above the dose indicated in 10 patients (Cases 2–5, 7, 11, 13–16). Side effects prevented a larger dose from being given in 5 patients, tiredness in 2 (Cases 9 and 10), one instance of nausea (Case 1), of indigestion (Case 12), and of headache (Case 8).

Effect on number of attacks of angina

The number of attacks experienced and trinitrin consumption, on each strength of propranolol, are given in Table 1. As dosage is increased from zero to full strength there is a progressive reduction in the number of attacks of angina. Except in the change from 1/8 to 1/4 strength, each individual increment results in a significant reduction of anginal attacks. The part of the dose response curve that can be plotted from the dosages used in this study is illustrated in Fig. 1. The pattern

TABLE 1 Attacks of angina and number of trinitrin* consumed (6 weeks on each strength)
(* Same as attacks of angina, except where indicated in parentheses)

Case No.	sex	age	Placebo	$\frac{1}{8}$ Dose	$\frac{1}{4}$ Dose	$\frac{1}{2}$ Dose	Full	Propranolol (mg/day)
1	M	54†	424 (429)*	347 (348)	327	248	211 (213)	400
2	M	62	74	54	58	35	25	280
3	M	63	48	39	20	19	12	400
4	M	53	57	34	32	25	22	480
5	M	54‡	39	37 (38)	42 (41)	38 (31)	37	160
6	F	55	22 (29)	18 (23)	19 (22)	18 (23)	20 (26)	1280
7	M	60	104	98	79	71	55	480
8	M	65	63 (65)	55 (56)	45 (47)	56 (59)	36 (33)	320
9	F	67	118 (39)	53 (28)	20 (15)	38 (22)	10 (8)	480
10	M	46	36	26 (27)	15 (13)	16	8	240
11	F	58	16 (17)	16	16	16	15	400
12	M	63	54 (57)	43 (45)	36 (37)	36 (37)	23 (25)	960
13	M	69	26	17	13	8	7	240
14	M	67	41	43	36	41	37	80
15	M	62	206 (218)	166 (142)	126 (87)	94 (52)	64 (35)	240
16	M	61	30	29 (27)	27 (26)	24	24 (25)	240
Attacks angina								
Mean (SE)			84.9 (25.5)	67.2 (20.8)	56.9 (19.4)	48.9 (14.4)	37.8 (12.3)	
			§P<0.001 P<0.01 P<0.20 P<0.0025					
Trinitrin consumed								
Mean (SE)			81.8 (26.5)	64.7 (20.5)	54.4 (19.0)	46.3 (14.1)	36.4 (12.2)	
			P<0.001 P<0.0025 P<0.10 P<0.0025					
Average dose			0	52 mg	104 mg	208 mg	417 mg	

† Severe pain on placebo only completed two cycles of trial, i.e. 4 weeks on each dose.

‡ Influenza in first cycle of trial – spent period in bed. Results from 2nd and 3rd cycle, i.e. 4 weeks on each dose.

§ Levels of P calculated from difference in log numbers of attacks on each strength in each patient (single-tail).

of consumption of trinitrin tablets was throughout almost identical. A progressive increase in the number of days that were pain free was seen as the dosage of propranolol

was increased (Table 2). All patients kept a full record of the number of attacks of pain and trinitrin consumption throughout. Of the 16, 14 (i.e. all except patients 3 and 16) kept a complete record of the duration of attacks of pain. This is summarized in Table 2. The average total duration of pain on placebo was over 3½ times that on full strength, and the average number of attacks of pain on placebo was 2½ times that on full strength propranolol. The greater difference when the total duration of pain is considered is particularly obvious in some patients who showed little difference in the number of attacks of pain, for instance Case 11 had pain for 4 times as long on placebo, Case 14 nearly 3 times as long on placebo as compared with the duration of pain on full strength.

The duration of individual attacks of pain is shown in Table 3. Pain tends to be shorter and less severe on propranolol, but these differences do not quite reach the 5 per cent level of significance (two-tail P test).

FIG. 1 Part of the dose response curve to propranolol on the number of attacks of anginal pain ($n = 16$).

TABLE 2 Number of days free of pain and total duration of anginal pain

	Average number of days pain free † in 6-week period (n=16)	Average total duration of pain (minutes) † in 6-week period (n=14)
Placebo	8.6 (SE 2.22) *P<0.05	413.7 (SE 111.0) P<0.0025
$\frac{1}{8}$ dose	12.7 (SE 2.52) P<0.01	212.8 (SE 61.4) P<0.005
$\frac{1}{4}$ dose	15.3 (SE 2.58) P<0.40	180.5 (SE 52.6) P<0.15
$\frac{1}{2}$ dose	15.9 (SE 2.76) P<0.001	161.8 (SE 44.6) P<0.005
Full dose	19.9 (SE 3.02)	115.6 (SE 29.6)

* P calculated as in Table 1 (single-tail).

† Cases 1 and 5 calculated on 4-week period.

Carry over The number of attacks of pain in the first and second weeks of each of the three two-weekly periods on each dose of propranolol has been analysed and is summarized in Table 4. The number of attacks of pain in the first and second week was closely similar on a particular strength of propranolol. When patients changed to placebo there was a small but significant negative 'carry over' effect from the previously administered propranolol, 11 patients experiencing more pain in the first than in the second weeks.

General subjective assessment and well-being The patients' general assessment of their angina over the previous two weeks has been awarded arbitrary scores, same 0, better 1, much better 2, worse -1, much worse -2. Several patients replied 'little worse' scored - $\frac{1}{2}$, 'little better' scored $\frac{1}{2}$. The average score on full dose propranolol was 1.5, placebo 0.6 (P<0.02 two-tail). The score on the half dose was 1.6, other values were intermediate.

Patients' replies to a question about the general sense of well-being were awarded

TABLE 3 Average duration (minutes) of individual attacks of pain (n=14)

	Weighted duration†	
Placebo	6.8 (SE 1.96) *P<0.10	13.8 (SE 5.45) P<0.10
$\frac{1}{8}$ dose	4.1 (SE 0.81)	6.54 (SE 1.04)
$\frac{1}{4}$ dose	4.0 (SE 0.74)	6.27 (SE 1.01)
$\frac{1}{2}$ dose	4.3 (SE 0.92)	6.44 (SE 1.10)
Full dose	4.1 (SE 0.85)	6.53 (SE 1.16)

* P calculated as in Table 1 but double-tail test (single-tail: P<0.05).

† Weighted duration, attacks listed as mild duration $\times 1$, moderate $\times 2$, severe $\times 3$.

scores, fair 0, well 1, very well 2, ill -1, very ill -2. Average scores on full strength 2.4, half and quarter strength were similar, eighth dose 1.1, placebo 1.3 (difference between full strength and placebo P<0.05 two-tail).

Weight Patients' weight did not vary throughout.

FIG. 2 Part of the dose response curve to propranolol on the supine and standing pulse rates (n=16).

TABLE 4 Carry over: attacks of angina 1st and 2nd week of each fortnight period (i.e. 3 'first' weeks, 3 'second' weeks each strength)

Greater no. of attacks pain	Placebo	$\frac{1}{8}$ Dose	$\frac{1}{4}$ Dose No. of patients	$\frac{1}{2}$ Dose	Full dose
1st weeks	11	5	7	7	8
2nd weeks	3	10	7	7	6
No difference	2	1	2	2	2
Average no. attacks					
1st weeks	44.3 (SE 13.4)	39.9 (SE 10.7)	28.8 (SE 9.9)	25.4 (SE 7.3)	18.9 (SE 5.5)
2nd weeks	*40.6 (SE 12.1)	34.3 (SE 10.2)	28.1 (SE 9.6)	23.5 (SE 7.1)	19.0 (SE 6.8)

* Difference between first and second weeks on placebo P<0.02 (two-tail) calculated from actual numbers (not logs) in view of several low numbers involved.

Pulse rate Table 5A shows that there is a steady slowing of the pulse as dose of propranolol is increased and there is a progressive reduction of increase in pulse rate on changing from the supine to standing position. Fig. 2 shows the part of the dose response curve for both supine and standing pulse rates. A similar reduction in pulse rate is observed when hypertensive patients are analysed separately (Table 5B).

Blood pressure The blood pressures of all patients, supine and standing, and hypertensives (diastolic pressures over 90 mmHg, on placebo $n=6$) are given in Table 5B. The blood pressure fell as dose of propranolol was increased, 11 mmHg drop supine, 12 mmHg drop standing for the hypertensives. There was no further drop in the hypertensives when propranolol was increased from half to full strength. The attacks of angina for the normotensives and hypertensives have been analysed separately and are also given in Table 5B. The blood pressures after the simple exercise test were similar to the standing pressures, and there was no exercise hypotension.

Effect of trinitrin on blood pressure In the 6 patients studied 0.5 mg sublingual of trinitrin produced an average maximum fall of mean supine pressure of 13 mmHg and of standing pressure 21 mmHg, on placebo

TABLE 5A Average pulse rate ($n=16$)
(3 readings each strength, except
Cases 1 and 5, two readings)

	Supine	Standing	Standing-supine
Placebo	83.8 (SE 2.59) * $P<0.001$	95.8 (SE 2.39) * $P<0.001$	12.0 (SE 1.30) † $P<0.45$
½ dose	71.1 (SE 3.07) $P<0.025$	81.3 (SE 3.40) $P<0.001$	10.2 (SE 1.21) $P<0.05$
¼ dose	67.9 (SE 2.43) $P<0.0025$	76.3 (SE 2.39) $P<0.001$	8.6 (SE 1.11) $P<0.10$
½ dose	63.7 (SE 2.84) $P<0.10$	71.3 (SE 2.57) $P<0.0125$	7.6 (SE 0.8) $P<0.15$
Full dose	61.4 (SE 2.17)	67.6 (SE 3.20)	‡ 6.2 (SE 1.1)

* P calculated as in Table 1 (single-tail).

† P calculated from actual numbers in view of low numbers.

‡ P for full versus placebo $P<0.005$ (two-tail).

tablets. The fall was 12 mmHg supine and 17 mmHg standing on full strength propranolol, 10 mmHg supine, 17 mmHg standing on half strength propranolol. These differences between propranolol and placebo were not significant.

Acute exercise tests As dose of propranolol was increased there was an increase in the amount of work that could be performed in an acute exercise test before the onset of pain, though there was no significant change in duration of pain after the end of exercise

FIG. 3 Example of the effect of propranolol on the electrocardiogram (Case 12) at rest and on exercise.

TABLE 5B Blood pressure (mmHg) all patients, BP, pulse (/min), and angina attacks in hypertensives $n=6$ (3 readings each strength except Cases 1 and 5 (normotensives) 2 readings)

	All patients ($n=16$)		Supine	Pulse	Hypertensives ($n=6$)		Attacks angina
	Supine	Standing			Supine	Standing	
	Mean BP	Mean BP	Mean BP		Mean BP	Pulse	
Placebo	107 (149/86) *NS	98 (130/82) $P<0.01$	130 (182/103) NS	86.2 $P<0.001$	115 (154/96) $P<0.10$	98.3 $P<0.0025$	48 $P<0.05$
$\frac{1}{8}$	105 (146/85) NS	95 (125/80) $P<0.10$	126 (172/103) NS	73.0 $P<0.01$	110 (142/94) NS	83.7 $P<0.001$	40 $P<0.05$
$\frac{1}{4}$	103 (144/83) $P<0.10$	93 (123/78) $P<0.10$	121 (171/99) NS	67.8 $P<0.025$	107 (141/90) $P<0.05$	75.8 $P<0.0125$	35 $P<0.10$
$\frac{1}{2}$	100 (140/79) NS	90 (120/75) NS	119 (168/94) NS	63.8 $P<0.025$	102 (135/85) NS	72.0 $P<0.025$	32 $P<0.10$
Full	98 (139/78)	89 (120/73)	119 (167/94)	60.5	103 (137/86)	67.3	27
Difference placebo versus full-strength P two-tail P							
	$P<0.001$	$P<0.001$	$P<0.02$	$P<0.001$	$P<0.005$	$P<0.001$	$P<0.001$

* Single-tail P calculated as in Table 1.

NS = not significant $P>0.10$, $P<0.10$ indicated.

(Table 6A). The resting pulse rate, the rate after the start of exercise, and at the end of exercise (i.e. onset of chest pain) are given in Table 6B.

In the 8 patients in whom it was possible to measure ST segment depression there was a significant reduction in depression at rest as the dose of propranolol was increased (Table 7). At the onset of anginal pain and when the pain disappeared changes were not significant. An example of an individual patient (Case 12) is illustrated by Fig. 3.

Discussion

Effect on angina The present study has shown that there is a dose-dependent reduction of attacks of angina pectoris from propranolol (Table 1). The part of the dose response curve that can be plotted (Fig 1) is part of the portion of the curve that typically rises in a linear manner. There is no flattening of the slope that is a characteristic response to dosage approaching that required for maximum effect. This is evidence that a further increase in dosage, when this can be tolerated, might result in a further reduction in angina attacks. Progressive benefit is confirmed by the reduction in trinitrin consumption (Table 1), reduction in the total duration of pain experienced (Table 2), increase in the number of pain-free days (Table 3), all indices showing maximum effect with the largest dose. Patients had an increased feeling of well being on propranolol.

No evidence was found of carry over of drug effect after stopping propranolol treatment (Table 4). Acute exercise tests also show a progressive increase in work done as dosage of propranolol is increased (Table 6A).

Effect on pulse rate and blood pressure

As the dose of propranolol is increased there is a progressive fall of the supine and standing pulse rates with a progressive reduction in the increase in the acceleration of the pulse rate on changing from the supine to the

TABLE 6A Acute exercise tests: average work of exercise in $kWsec$ $n=10$ (average 2 readings each patient, each strength)

Placebo	$\frac{1}{8}$	$\frac{1}{4}$	$\frac{1}{2}$	Full dose
13.28 (100%) (SE) (4.10)	§14.22 (115%) (4.17) $P<0.15†$	15.37 (126%) (4.56) $P<0.05$	‡14.86 (137%) (3.01) $P<0.30$	17.10 (148%) (4.32) $P<0.20$

Difference between placebo and full strength $P<0.01$.*

(P calculated as in Table 1 *two-tail, †single-tail value for P).

‡ 7 out of 10 patients exercised longer on $\frac{1}{2}$ strength than $\frac{1}{4}$ strength, lower average on $\frac{1}{4}$ strength due to one patient showing a considerably greater duration of exercise on $\frac{1}{4}$ strength.

§ Expressed as a percentage, placebo = 100 per cent average from readings on each patient.

Average duration of pain (sec)

206 (SE) (67.2)	167 (48.0)	211 (94.7)	163 (52.9)	196 (66.5)
None of differences are significant				

standing position (Table 5A and B). Similarly to the dose response curve for anginal attacks, the dose response curve for pulse rate, supine and standing (Fig 2), shows a linear increase in effect for increase in dose with no flattening of the curve, indicating that a near maximum effect had not been reached. At the time of the acute exercise tests the progressive reduction in the resting pulse rate was also observed (Table 6B); there was also a fall in the tachycardia on exercise with a progressive reduction in the increase in pulse rate at the time of onset of pain. The progressive differences between the various dose levels of propranolol are clearer under higher levels of sympathetic activity, i.e. exercise, than at rest, a state of low sympathetic activity.

Propranolol lowers the blood pressure, and we have reported its use in hypertension (Prichard and Gillam, 1964, 1969). The effect of progressive increase of dose is shown in Table 5B. In the 6 hypertensive patients increasing the dose from zero to half strength progressively lowered the blood pressure, but doubling the dose to full strength had no further effect.

Patients receiving propranolol did not appear to experience any excess hypotensive effect from trinitrin.

Effect on ST segment changes Propranolol produces progressively less ST segment depression at rest as dosage is increased, whereas the change in the ST depression at the time of pain did not reach the levels of significance. However, intravenous studies have shown a significant reduction in ST segment depression at the onset of anginal pain (Prichard, Aellig, and Richardson, 1970).

Action of propranolol in angina It seems likely that propranolol exerts its benefit in angina by virtue of its inhibition of the sympathetic to the heart.

Those beta-receptor blocking drugs without local anaesthetic action have been found to exert anti-anginal effect—practolol after intra-

TABLE 6B *Acute exercise tests: average pulse rates (n=10 average 2 readings each patient, each strength)*

		Resting	Exercise + 1 min	At onset pain
Placebo		78.6 (SE 2.99)	101.7 (SE 1.60)	113.8 (SE 2.84)
	*P	<0.0025	<0.0025	<0.0025
$\frac{1}{8}$ dose		69.4 (SE 2.27)	89.8 (SE 2.42)	99.0 (SE 3.40)
	*P	<0.25	<0.0025	<0.005
$\frac{1}{4}$ dose		68.2 (SE 2.52)	83.8 (SE 2.61)	94.5 (SE 2.69)
	P	<0.0025	<0.005	<0.05
$\frac{1}{2}$ dose		62.9 (SE 2.21)	79.1 (SE 2.22)	91.9 (SE 2.81)
	P	<0.25	<0.25	<0.05
Full dose		62.1 (SE 2.07)	78.4 (SE 2.25)	89.0 (SE 2.77)

* Single-tail P calculated as in Table 1.

venous administration (Areskog and Adolfs-son, 1969; Wilson *et al.*, 1969; Prichard *et al.*, 1970) or after oral administration (George, Nagle, and Pentecost 1970; Prichard, Lionel, and Richardson 1971), and sotalol after intravenous administration (Prichard *et al.*, 1970). In addition, Wilson *et al.* showed that the D-isomer of propranolol, which has no beta-blocking action, had no anti-anginal activity, though it has equal local anaesthetic effect to propranolol in the ordinary DL form. Reduced perception of pain from some local anaesthetic (or central) action from propranolol as a basis for its anti-anginal action is also rendered unlikely by the observation that the increase in work after propranolol is not at the expense of increased ST depression on exercise: the contrary in fact occurs (Prichard *et al.*, 1970).

Conclusions

For maximum effectiveness in relieving the symptoms of angina the dosage of propranolol should be increased so that the dose finally used is either that which completely relieves symptoms or is just below that which produces side effects.

Sensitivity to propranolol varies considerably and dosage is best started at 10 mg q.d.s.; increases may be made as frequently as the patient is seen, usually weekly or fort-

TABLE 7 *Acute exercise tests: ST segment depression (mm) (n=8 average 2 readings each patient, each strength)*

	Placebo	$\frac{1}{8}$ Dose	$\frac{1}{4}$ Dose	$\frac{1}{2}$ Dose	Full dose
At rest (SE)	0.81 (0.24)	0.92 (0.47)	0.51 (0.28)	0.46 (0.25)	0.31 (0.24)
	(difference between placebo and full dose: P < 0.005)				
At onset of pain (SE)	2.70 (0.43)	2.47 (0.50)	2.25 (0.38)	2.66 (0.78)	2.34 (0.60)
	(difference between placebo and full dose: P < 0.30)				
At pain gone (SE)	1.26 (0.14)	1.25 (0.23)	0.85 (0.13)	1.13 (0.31)	1.09 (0.29)
	(difference between placebo and full dose: P < 0.40)				

P (two-tail) calculated from actual numbers in view of low numbers.)

nightly, but in view of the short half-life of propranolol there seems no reason why this should not be more frequent.

We are grateful to Mr. B. R. Graham for technical assistance and for drawing the diagrams, to Miss Ruth Swanton for secretarial assistance, and to Miss Valerie Price for assistance with the calculations.

References

- Areskog, N. H., and Adolfsson, L. (1969). Effects of a cardioselective beta-adrenergic blocker (I.C.I. 50172) at exercise in angina pectoris. *British Medical Journal*, **2**, 601.
- George, C. F., Nagle, R. E., and Pentecost, B. L. (1970). Practolol in treatment of angina pectoris. A double-blind trial. *British Medical Journal*, **2**, 402.
- Gianelly, R. E., Goldman, R. H., Treister, B., and Harrison, D. C. (1967). Propranolol in patients with angina pectoris. *Annals of Internal Medicine*, **67**, 1216.
- Gillam, P. M. S., and Prichard, B. N. C. (1965). Use of propranolol in angina pectoris. *British Medical Journal*, **2**, 337.
- Gillam, P. M. S., and Prichard, B. N. C. (1966). Propranolol in the therapy of angina pectoris. *American Journal of Cardiology*, **18**, 366.
- Ginn, W. M., and Orgain, E. S. (1966). Propranolol hydrochloride in the treatment of angina pectoris. *Journal of the American Medical Association*, **198**, 1214.
- Grant, R. H. E., Keelan, P., Kernohan, R. J., Leonard, J. C., Nancekivell, L., and Sinclair, K. (1966). Multicenter trial of propranolol in angina pectoris. *American Journal of Cardiology*, **18**, 361.
- Hamer, J., Grandjean, T., Melendez, L., and Sowton, G. E. (1964). Effect of propranolol (Inderal) in angina pectoris. *British Medical Journal*, **2**, 720.
- Harley, B. J. S., and Davies, R. O. (1968). Propranolol in the office treatment of angina pectoris. *Canadian Medical Association Journal*, **99**, 527.
- Hebb, A. R., Godwin, T. F., and Gunton, R. W. (1968). A new beta adrenergic blocking agent, propranolol, in the treatment of angina pectoris. *Canadian Medical Association Journal*, **98**, 246.
- Keelan, P. (1965). Double-blind trial of propranolol (Inderal) in angina pectoris. *British Medical Journal*, **1**, 897.
- Mizgala, H. F., Khan, A. S., and Davies, R. O. (1969). Propranolol in the prophylactic treatment of angina pectoris. *Canadian Medical Association Journal*, **100**, 756.
- Prichard, B. N. C., Aellig, W. H., and Richardson, G. A. (1970). The action of intravenous administration of oxprenolol, practolol, propranolol and sotalol, on acute exercise tolerance in angina pectoris, the effect on pulse rate and the electrocardiogram. *Postgraduate Medical Journal*, **46** (Nov. Suppl.) 77.
- Prichard, B. N. C., and Gillam, P. M. S. (1964). Use of propranolol in treatment of hypertension. *British Medical Journal*, **2**, 725.
- Prichard, B. N. C., and Gillam, P. M. S. (1969). Treatment of hypertension with propranolol. *British Medical Journal*, **1**, 7.
- Prichard, B. N. C., Lionel, N. W. D., and Richardson, G. A. (1971). Comparison of practolol and propranolol in angina pectoris. *Postgraduate Medical Journal*, **47** (Jan. Suppl.), 59.
- Rabkin, R., Stables, D. P., Levin, N. W., and Suzman, M. M. (1966). The prophylactic value of propranolol in angina pectoris. *American Journal of Cardiology*, **18**, 370.
- Wilson, A. G., Brooke, O. G., Lloyd, H. J., and Robinson, B. F. (1969). Mechanism of action of β -adrenergic receptor blocking agents in angina pectoris; comparison of action of propranolol with dexpropranolol and practolol. *British Medical Journal*, **4**, 399.
- Wolfson, S., Heinle, R. A., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R. (1966). Propranolol and angina pectoris. *American Journal of Cardiology*, **18**, 345.