

CLINICAL EXPERIENCES WITH PROPRANOLOL

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ADRENERGIC beta-receptors are responsible for the cardiac effects of the sympathetic nervous system (Ahlquist, 1948). Pronethalol (Black and Stephenson, 1962) first proved to be an effective beta-receptor blocking agent with little sympathomimetic activity. Limited clinical trials suggested that pronethalol was of value in angina (Dornhorst and Robinson, 1962; Alleyne and colleagues, 1963; Barnett and Brandstater, 1964), in arrhythmias including those attributed to digitalis (Stock and Dale, 1963) and those occurring during anaesthesia (Payne and Senfield 1964; Johnstone, 1964). The drug was also used in phaeochromocytoma (Dornhorst and Laurence, 1963), in hypertrophic obstructive cardiomyopathy (Harrison, Ross, Chidsey and Braunwald, 1963; Cohen, Effat, Goodwin, Oakley and Steiner, 1964), in hypertension (Prichard, 1964), in Parkinsonian tremor (Herring, 1964), and in metaraminol-treated hypotension (Luria, Miller and Kaplan, 1964). However, the clinical use of pronethalol has been limited by its side-effects in man and by its toxic properties in mice (Paget, 1963). A further analogue, propranolol (I.C.I. 45520; Inderal) (Black, Crowther, Shanks, Smith and Dornhorst, 1964) did not appear to have these undesirable properties. We are reporting our experiences with the clinical use of propranolol with particular reference to its use in arrhythmias, in angina pectoris and during anaesthesia, and to its effect on the blood lipid picture and its toxicity.

Material and Methods

Fifty-six patients were treated with propranolol for a variety of conditions. In thirty-eight patients the drug was used for its anti-arrhythmic properties, in sixteen it was given to patients suffering from angina; it was also used in two patients with other conditions. Of the fifty-six patients, forty-seven received propranolol on a long-term basis in a dosage that varied from 30 mg. to 80 mg. daily in 3 or 4 divided doses. Up to 220 mg. was given on a single day. The longest duration of treatment was ten months.

Patients receiving propranolol were checked clinically at frequent intervals and blood was taken for certain haematological and biochemical investi-

gations. These were: white blood count (WBC), transaminases (SGOT, SGPT) (Reitman and Frankel, 1957), lactic dehydrogenase (LDH) (Wroblewski and LaDue, 1955), blood urea, bilirubin (by the method of Malloy and Evelyn), alkaline phosphatase (autoanalyser) (Marsh, Fingerhut and Kirsch, 1959), and thymol turbidity (by the method of MacLaggan).

Eleven of the patients on long-term propranolol were also investigated for changes in certain blood lipid fractions. Three of these patients were receiving the drug for prevention of arrhythmias and the remainder were suffering from angina. The blood samples were taken either fasting from in-patients or were taken at noon from out-patients who had had a light breakfast and rested for half-an-hour before venepuncture. In any one patient, all the samples were either taken as an in-patient or all the samples as an out-patient. Blood was withdrawn from an antecubital vein without proximal constriction of the arm. The lipid fractions measured were as follows: total cholesterol by the method of Zak and Zlatkis (Leffler, 1960), phospholipids by the modified Bartlett method (Bartlett, 1959), triglycerides (Handel and Zilversmit, 1957) and free fatty acids by the technique of Dole (1956).

Propranolol has been used during anaesthesia in fifty patients by Dr. H. L. T. Thornton and Dr. L. Strunin and we are grateful to them for some details of their results which we report in the section on the use of propranolol in anaesthesia.

Results

Reversion of Arrhythmias to Sinus Rhythm (10 patients)

Supraventricular Tachycardia. Ten episodes in five patients have been corrected. In all except one the patients were referred because the tachycardia had proved resistant to the usual forms of treatment. Two patients were in congestive cardiac failure due to the arrhythmia which had lasted for three and ten days respectively. In both patients sinus rhythm was restored after one oral dose of propranolol, 10 mg. The largest oral dose needed in any of the patients was 40 mg. One patient who developed a supraventricular tachycardia during anaesthetic induction for cardiac surgery had undergone previous cardiac surgery and the procedure had been made extremely difficult by recurrent tachycardia. With the second operation however 1 mg. of propranolol given intravenously stopped the tachycardia and this

did not recur during a seven hour operation. Propranolol alone failed to revert a second episode of supraventricular tachycardia in one patient but carotid sinus pressure, that had been ineffective before the drug, caused reversion to sinus rhythm one hour after an oral dose of 20 mg.

Ventricular Tachycardia. Five episodes in three patients have been corrected using oral propranolol 20 mg. in four instances. The fifth episode occurred during cardiac catheterisation and reverted within one minute of giving 5 mg. of propranolol intravenously. None of these patients with ventricular tachycardia was in congestive failure or markedly hypotensive when treated.

Atrial Flutter and Atrial Fibrillation. One patient with untreated thyrotoxicosis and atrial flutter was digitalised. In view of the rapid ventricular rate propranolol was recommended. However, when treatment was started, atrial fibrillation had developed and, after three days therapy, sinus rhythm was restored.

No deliberate attempts have been made to use propranolol for the restoration of sinus rhythm in atrial fibrillation and there is no evidence that propranolol is of any value in this respect.

Ventricular Fibrillation. One case-history is recorded.

A woman of 60 was being treated with sustained action isoprenaline for complete heart block and occasional Adams-Stokes attacks. After three months on this drug she had a further syncopal episode and was then given an extra tablet of sustained action isoprenaline. After one hour the patient started to have frequent syncopal attacks and was admitted to hospital where an electrocardiogram demonstrated recurrent paroxysms of ventricular fibrillation. Over the succeeding two hours 60 mg. of propranolol were given, the first 10 mg. intravenously. During this time the Adams-Stokes attacks diminished in frequency and finally ceased.

Prevention of Recurrent Arrhythmias (20 patients)

Paroxysmal Supraventricular Tachycardia. Five patients were treated with propranolol in an attempt to prevent frequently recurring episodes of supraventricular tachycardia. The initial dose used was 10 mg. four times daily. Two of these patients are of special interest and are reported in some detail.

A man of 23 presented with a history of recurrent supraventricular tachycardia since infancy. His ECG demonstrated an intermittent Wolff-Parkinson-White pattern when in sinus rhythm. He had signs of a congenital ventricular septal defect. When first seen an attack of tachycardia had been present

for ten days and he was in gross congestive heart failure. The arrhythmia was corrected with a single oral dose of 10 mg. propranolol. In the preceding three months he had not been free from paroxysms for more than five days but on 40 mg. of propranolol daily he remained in sinus rhythm until the twelfth day of treatment when tachycardia recurred. On the fifteenth day he was re-admitted and was given two slow intravenous injections of 5 mg. of propranolol. After the second injection he reverted to sinus rhythm but thereafter oral propranolol up to 220 mg. daily did not appear to have any effect on preventing or reverting paroxysms of tachycardia.

A man of 60 presented with a twenty year history of paroxysmal supraventricular tachycardia. In the months before treatment he was having one to two attacks daily. The first observed episode was corrected by 40 mg. of oral propranolol. Thereafter he received 40 mg. of the drug daily and remained free of attacks for eighteen days. Between the 18th and 24th day of treatment the episodes recurred with increasing frequency, and after the 24th day in spite of increasing the dose of propranolol to 100 mg. daily, the drug did not appear to have any effect on the incidence or duration of the paroxysms.

In the three remaining patients, who had less frequent episodes of tachycardia, propranolol likewise failed as a long-term prophylactic agent.

Paroxysmal Atrial Fibrillation. Two patients were treated. In one, 30 mg. of propranolol daily prevented episodes of atrial fibrillation for one week, but thereafter up to 80 mg. daily failed to influence the incidence of the episodes. In the second patient, observed during three months of propranolol therapy, episodes of fibrillation appeared to become less frequent but the slower ventricular rate during the paroxysms provided relief and made recognition of attacks less accurate.

Frequent Ectopic Beats. Propranolol was used in three patients who had a history of ventricular ectopic beats for several years; one suffered from chronic rheumatic and the other from ischaemic heart disease. As both were out-patients they were only seen at monthly intervals and there was no reduction in the incidence of the ectopic beats. The third patient developed frequent ectopic beats after cholecystectomy; she had previously suffered from this arrhythmia intermittently for many years. The post-operative ectopic beats were abolished during the one week period of treatment and observation.

Prevention of Relapse after Reversion of Atrial Fibrillation by Direct Current Shock. Ten patients were given propranolol in an attempt to prevent relapse into atrial fibrillation after direct current (DC) shock had been used

TABLE 1
 PROPRANOLOL GIVEN IN AN ATTEMPT TO MAINTAIN
 SINUS RHYTHM AFTER REVERSION OF ATRIAL FIBRILLATION BY D.C. SHOCK

Age	Diagnosis	Duration A. Fib.	Operation	C.T.R.	Present state
52	M.S.	6 months	Yes	54%	S.R.—5 months
49	M.S.	6 months	Yes	50%	Relapse—4 hours
49	M.S.	13 months	Yes	52%	Relapse—3 weeks
40	M.S.	Parox 3 years Perm 5 weeks	Yes	53%	Relapse—2 months
38	Mild M.S.	Parox 6 months Perm 5 weeks	No	54%	S.R.—2 months
47	M.S., A.I.	5 weeks	No	61%	Relapse—10 weeks
55	M.I., M.S.	2 years	Yes (1962)	63%	Off Propranolol 1st day—long PR
56	“Lone” A.F.	5 months	No	50%	Off Propranolol 2nd day—asthma
53	M.S.	1 year	Yes	50%	Off Propranolol 1st day—long PR
49	M.S.	1 year	Yes	49%	Relapse—4 weeks

M.S. Mitral Stenosis. M.I. Mitral Incompetence. A.I. Aortic Incompetence.
 C.T.R. Cardio-thoracic Ratio. A.F. Atrial Fibrillation.

to revert atrial fibrillation to sinus rhythm (Lown, Amarasingham and Neuman, 1962). Patients were given 40 mg. per day in four divided doses starting the day before reversion and continued for three months. The results are shown in Table 1. The drug was discontinued in three cases, one because of an asthmatic wheeze, and two because of partial heart block. Of the other seven only two were in sinus rhythm at the end of a three month period.

Control of Heart Rate (6 patients)

Atrial Fibrillation. Propranolol was used in two patients with atrial fibrillation and a rapid ventricular rate despite adequate digitalization. In both cases the rate was reduced, in one from 140 to 110 and in the other from 120 to 95 per minute.

Sinus Rhythm. Of 22 patients in sinus rhythm, the average heart rate before propranolol was 92 and on treatment was 70 beats per minute.

Four patients with effort syndrome and sinus tachycardia were treated. These patients all complained of palpitation and, in spite of sedation, casual pulse rates recorded in the out-patient clinic averaged 130, 130, 110 and 100 respectively. On treatment with propranolol the pulse rate slowed and averaged 85, 80, 87, and 70 respectively, and only one of the patients still noticed palpitation and she found the symptom less marked. In one of these cases treatment was stopped and the heart rate then increased from 78 to 130. The slower rate was restored by further propranolol.

Use in Anaesthesia

Forty patients were given propranolol for

ventricular arrhythmias produced by anaesthetic agents. Halothane was the anaesthetic usually in use and ectopics were the commonest arrhythmia but occasionally short runs of ventricular tachycardia occurred. Parenteral propranolol proved immediately effective in abolishing these arrhythmias and also those associated with carbon dioxide retention and, in two cases, ectopic beats associated with a high serum potassium level. Propranolol also reduced the incidence of ectopic beats associated with intrathoracic surgery.

Propranolol was found to be useful in slowing the heart rate in certain surgical situations. Tachycardia is produced by adrenaline-containing saline injected locally to define tissue planes and this could be slowed effectively by propranolol. One patient developed reflex tachycardia during surgery in the region of the stellate ganglion and this was slowed by propranolol. The tachycardia of thyrotoxicosis showed some slowing with propranolol, and, if the tachycardia produced by atropine premedications was too marked, propranolol was effective in producing some slowing.

One patient under halothane anaesthesia was given a ganglion blocking agent to lower the blood pressure; subsequently 1 mg. of propranolol was given and this produced a marked hypotension which proved difficult to correct.

The dose used in all cases initially was 1 mg. given slowly intravenously. The largest dose used was 3 mg. The drug was usually effective within one minute.

Use in Ischaemic Heart Disease (16 patients)

Sixteen patients with angina pectoris were treated with 10 mg. of propranolol 3 or 4 times daily, increasing to 20 mg. 4 times daily

EFFECT OF LONG-TERM PROPRANOLOL ON BLOOD LIPID FRACTIONS

TABLE 2

Patient	Sex	Age	Diagnosis	In/Out Patient	Duration Treatment		Total Cholesterol	Phospholipid	Triglycerides	Free Fatty Acid
					1st sample	Final sample				
L.L.	M	63	I	I.P.	1d	2w	405 ±39	261 ±57	335 ±20	6.6 ±2.4
J.G.	M	69	I	I.P.	2d	5d	205 ±16	222 ±2	297 ±28	9.1 ±4.8
C.R.	M	62	I	O.P.	3w	4m	292 ±16	234 ±2	150 ±28	(5) ±4.8
J.C.	M	67	I	I.P.	5d	4m	182 ±12	251 ±30	97 ±14	4.3 ±1.0
E.B.	F	70	I	O.P.	1w	9w	342 ±14	339 ±8	788 ±14	13.8 ±1.0
L.L.	M	63	I	O.P.	1m	3m	394 ±24	292 ±16	178 ±14	(2) —
J.C.	M	67	I	O.P.	1w	10m	216 ±24	207 ±16	141 ±14	11.3 ±2.1
F.W.	M	48	R	O.P.	7m	9m	242 ±24	220 ±2	118 ±28	10.7 ±2.1
J.F.	M	44	I	O.P.	1w	3m	264 ±24	225 ±46	288 ±78	8.9 ±2.1
J.S.	F	49	R	I.P.	4d	—	210 ±16	206 ±16	177 ±16	18.4 ±2.1
A.K.	F	41	R	O.P.	2m	—	326 ±16	169 ±16	216 ±16	7.6 ±1.0
Average eleven patients							280(11)	235(11)	253(11)	9.7(10)
Significance of difference							0.5 > P > 0.4	0.3 > P > 0.2	0.5 > P > 0.4	0.2 > P > 0.1

I. Ischaemic heart disease.
 R. Arrhythmia.
 O.P. Out-patient.
 I.P. In-patient.
 d. Days.
 w. Weeks.
 m. Months.
 Results in mg./100 ml. Figures are averages; the number of readings that have been averaged is given in brackets followed by the standard deviation.

if there had been no beneficial effect. None of the sixteen showed significant objective or ECG improvement. Five patients reported a subjective impression of improvements and the other eleven reported no change.

We have not used propranolol in the treatment of any acute coronary occlusive episode.

Use in Cardiac Catheterisation

Five patients were given propranolol intravenously to correct arrhythmias developing during cardiac catheterisation. In four cases multiple ventricular ectopic beats were reduced in number but not abolished. One case of ventricular tachycardia was restored to normal rhythm.

Other Uses of Propranolol

Two other patients have been treated with long-term propranolol, one with hypertrophic obstructive cardiomyopathy, and one with thrombo-embolic pulmonary hypertension. In neither case was there enough objective evidence to show whether or not the drug was of benefit.

Effect of Propranolol on Blood Lipid Levels

The results obtained in the eleven patients tested are summarized in Table 2. The "control" samples were taken either before starting propranolol or more than one week after discontinuing the drug. The "treatment" blood samples were taken at any time from one day to ten months after starting the drug, and the duration of treatment at the time of taking the first and last sample is shown in each case.

Toxicity

Hæmatology and Biochemistry

The results of tests carried out on patients taking long-term propranolol are summarized in Table 3.

Three of these results caused some concern. The two abnormal white counts, one of 14,000/cu. mm. (neutrophils 9,000) and one of 15,000/cu. mm. (neutrophils 11,200), occurred five weeks and seven months respectively after starting propranolol. Neither patient showed any other obvious cause for the leucocytosis, both had previous and subsequent normal white counts during continued therapy. The third result that caused concern was a SGPT result of 108 units/ml. The patient was a known asthmatic and was receiving 30 mg. daily of propranolol as well as digoxin for paroxysmal atrial fibrillation. After four weeks the dose was raised to 60 mg. daily. Four weeks later she complained of some increase in breathlessness and was found to be in atrial fibrillation

with the JVP 3 cm. +. Her body weight had increased 4 lbs., her chest was clear clinically and on X-ray, with no increase in heart size. It was on this day that her SGPT was 108 units/ml. SGOT and urea the same day were normal and continuing the same dose of propranolol together with an oral diuretic improved the breathlessness. All biochemical tests proved normal on three subsequent occasions.

The remaining abnormal results were found in situations in which there was another more likely cause. Four of the abnormal SGPT results occurred in two patients in congestive cardiac failure (from supraventricular tachycardia and thrombo-embolic pulmonary hypertension) and one of the SGPT results and the abnormal SGOT occurred immediately after DC shock for conversion of atrial fibrillation to sinus rhythm. Eight of the abnormal blood urea levels occurred in three patients in whom similar urea values were found while not on propranolol. When one patient became hypotensive on propranolol his blood urea rose from 40 to 50 mg./100 ml. The patient with thrombo-embolic pulmonary hypertension and congestive failure presented another of the abnormal urea results and the abnormal bilirubin (2.4 mg./100 ml.). Finally the patient who suffered multiple Adams-Stokes episodes produced a blood urea of 54 mg./100 ml. and a SGPT of 45 units/ml. two days after the episodes, but these subsequently returned to normal despite continued propranolol therapy.

Asthma (7 patients)

Four patients with known bronchial asthma were given long-term propranolol for cardiac conditions. None of them suffered an acute episode severe enough to need treatment. One noticed no difference in his breathing, two noticed their breathing was a little "tighter" but not troublesome, and the fourth developed slight wheeze with rhonchi the day following DC shock for reversion of his atrial fibrillation and propranolol was then discontinued.

Three other patients, who suffered from chronic bronchitis as well as angina pectoris, developed acute bronchitis while taking propranolol. During the attack of bronchitis they presented a mild wheeze with widespread rhonchi. The wheeze and rhonchi disappeared after control of the bronchitis with antibiotics and while continuing propranolol.

Skin Lesions (2 patients)

Treatment in two cases was discontinued because of skin reactions. Both patients complained of an itch felt on trunk and limbs two

TABLE 3
TOXICITY TESTS ON PATIENTS TAKING PROPRANOLOL

Test	No. of Patients	No. of Estimations	Upper limit of normal	No. of Abnormal Results	Patients with Abnormalities
W.B.C.	21	61	11,000/c. mm.	2	2
S.G.O.T.	27	75	40 U./ml.	1	1
S.G.P.T.	27	72	40 U./ml.	7	5
L.D.H.	23	62	500 U./ml.	1	1
Bl. Urea	24	66	40 mg./100 ml.	11	6
S. Bilirubin	14	30	0.8 mg./100 ml.	1	1
S. Alk. Phosphatase	15	31	15 Units	0	0
Thymol Turbidity	14	28	4 Units	0	0

and seven weeks after commencing treatment. The irritation gradually increased over the next three weeks and in one case this then disappeared after stopping propranolol. The other case then developed a fine scaly rash in the following two weeks and this disappeared on stopping the drug.

Gastro-Intestinal Side-Effects (2 patients)

In one patient nausea and vomiting occurred on the second day of treatment with propranolol 40 mg. daily. This lasted a few hours and did not recur on continuing the drug. Another patient, who had been reverted to sinus rhythm by DC shock, became nauseated with vomiting when she developed congestive failure associated with relapse into atrial fibrillation; the propranolol was discontinued but the nausea continued until her congestive failure was controlled.

Hypotension (3 patients)

Three patients needed adjustment of the dose of propranolol because of hypotension.

A man of 50 with angina and multifocal ventricular ectopic beats was given 30 mg. of propranolol daily for four months. His initial blood pressure was 150/90 mm. Hg. and at the end of the four months was 140/90. The dose was raised to 40 mg. per day and after one week the pressure fell to 100/68. The dose was lowered again to 30 mg. daily and the pressure returned to 120/90.

A man of 50 with angina was started on 30 mg. daily of propranolol. His initial pressure was 130/80 and after one week of treatment was 120/80. For the next week he received 40 mg. per day and his blood pressure dropped to 100/60 but rose again to 120/70 on reducing the dose of propranolol to 30 mg. daily.

A woman of 67 was being treated for paroxysmal atrial fibrillation with propranolol 40 mg. daily. Her initial blood pressure was 130/80 and it remained at this level for two months. In the third month of treatment the pressure gradually became lower and the drug was discontinued when the systolic level reached 80 mm. Hg. It later became evident that she had impairment of hepatic function from metastatic carcinoma.

We did not use propranolol specifically for the treatment of hypertension. Excluding the

three patients reported above, sufficient casual blood pressure readings were available for comparison before and during treatment in 18 patients with doses of propranolol from 30 mg. to 80 mg. daily. The average pressure before treatment was 157/87 mm. Hg. and while taking propranolol was 151/87 mm. Hg.

Congestive Heart Failure (7 patients)

Three patients with congestive failure due to long paroxysms of tachycardia recovered from their failure with reversion to sinus rhythm. Two other patients with some degree of congestive failure were treated with propranolol without any obvious deterioration. In one patient who had suffered from left ventricular failure due to acute cardiac infarction, propranolol was later used to revert two episodes of ventricular tachycardia, occurring three and four weeks after the initial infarct. Following the second episode of ventricular tachycardia he was given propranolol 50 mg. daily by mouth. After six days he developed further ischaemic pain and congestive failure and died the following day presumably from a second cardiac infarct. One patient developed congestive failure when she relapsed into atrial fibrillation ten weeks after successful DC defibrillation.

The body weights of 22 patients measured before starting propranolol, and during treatment with 30 mg. to 80 mg. daily for three to ten months showed that 20 of these patients' weights remained constant (less than 4 lbs. change) but two showed a marked increase. These were both patients who received propranolol 40 mg. per day following successful conversion of atrial fibrillation to sinus rhythm by DC shock. In the three months of prophylactic treatment their weights increased by 16 lbs. and 21 lbs. respectively. Their appetites were increased, there were no signs of congestive failure, and chest X-rays showed no increase in heart size or of pulmonary venous congestion.

Anticoagulant Regulation

Because one patient who was anticoagulated developed hæmaturia ten days after starting propranolol, we have reviewed the effect of propranolol on anticoagulant control. Sixteen patients were receiving anticoagulants at the time of starting propranolol and were under satisfactory control. The patient mentioned above was the only one who had a marked change in the prothrombin time or anticoagulant requirement during the first three weeks of treatment.

Treatment Discontinued

Toxic side effects necessitated withdrawal of propranolol in six patients: two developed rashes, one hypotension, and three following DC shock defibrillation who developed partial heart block (2 cases) or asthma (1 case).

Discussion

In our experience the greatest value of propranolol has been its acute anti-arrhythmic action. Oral propranolol may now prove to be the drug of choice for reversion of paroxysms of supraventricular tachycardia.

Only one of these patients was very ill with congestive failure, hypotension and vomiting, due to long-standing tachycardia and required intravenous therapy. Two doses of 5 mg. of propranolol were injected slowly, twenty minutes being taken over each injection with an hour between them and there were no apparent ill-effects. However this was our only experience with this type of case and others have reported near-fatalities with intravenous propranolol in hypotensive patients with congestive failure (J. Somerville, personal communication, 1964). Extreme caution is needed in the intravenous use of propranolol in hypotensive patients and in general we prefer DC shock.

The treatment of choice in cases of ventricular tachycardia is debatable and we must await further experience with propranolol and DC shock before the relative effectiveness and safety of these methods can be compared with those of procainamide and quinidine. When a drug can be given by mouth, propranolol appears to be safe and effective. It is our policy at present to give propranolol to these patients and to reserve DC shock for those who fail to respond to propranolol and for those patients too ill to take the drug orally.

The reversion of atrial fibrillation and flutter to sinus rhythm we believe is best achieved

by use of DC shock (Lown and others, 1962; Oram and Davies, 1964; McDonald, Resnekov and O'Brien, 1964).

The case of Adams-Stokes episodes associated with paroxysmal ventricular fibrillation is of interest. The appearance of ventricular fibrillation in this patient was attributed to excessive sustained action isoprenaline. With the more widespread use of this drug (Dack and Robbin, 1961; Fleming and Mirams, 1963) in the treatment of heart block, this becomes a situation in which an effective beta-receptor blocking drug has an important role.

Propranolol has proved less effective when given in an attempt to maintain sinus rhythm in patients with paroxysmal arrhythmias. The two case histories of such patients suggest tolerance of propranolol developing between the twelfth and twenty-fourth day of treatment. Similarly in one of the cases of paroxysmal atrial fibrillation, propranolol appears to become ineffective after one week. Stock and Dale (1963) noted this lack of maintenance of improvement when using pronethalol, and in cases treated by bilateral upper dorsal sympathectomy, a similar "escape" from treatment has been noted (White, Smithwick and Simeone, 1952).

We have therefore abandoned propranolol as a prophylactic agent in recurrent arrhythmias. It is of interest that D. A. Chamberlain (personal communication) has reported two cases who had temporary relief only after a sympathectomy and have now been treated with a beta-blocking drug for 18 months with sustained improvement and have no apparent tendency to "escape". Likewise our limited experience with frequent ectopic beats suggests that propranolol is of no value for long-term control. However there is little doubt that the temporary foci of ectopic beats can be controlled by propranolol. Multiple ectopic beats following acute cardiac infarction have not been treated with propranolol owing to the theoretical hazards of depressing myocardial function. If these risks should prove more theoretical than real, this situation would be an indication for the use of the drug.

The use of propranolol as a prophylactic agent after DC shock reversion of atrial fibrillation to sinus rhythm has also proved ineffective. The disappointing results summarized in Table 1 taken together with our doubts concerning the drug's sustained effect and the report of Tsolakas, Davies and Oram (1964) have caused us to abandon the use of propranolol for this purpose.

Propranolol has proved of value in slowing a rapid ventricular rate in two patients with atrial fibrillation who were fully digitalised. No tolerance or "escape" has been seen in this circumstance. However some such patients may be in border-line heart failure and the use of the drug might then be dangerous. Stock and Dale (1963) reported increasing heart failure due to beta-receptor blockade.

Propranolol slowed the heart rate of patients in sinus rhythm as did pronethalol (Dornhorst and Robinson, 1962). This action was likewise sustained over a period (in one of our patients up to eight months). We are unable to explain the sustained effects of propranolol in sinus tachycardia and atrial fibrillation as opposed to its diminishing efficacy in paroxysmal arrhythmias and long-standing ectopic beats.

The value of propranolol in angina pectoris is not as yet known and must await the results of a controlled series. The drug appears to improve exercise tolerance in some anginal patients in acute experiments (Hamer, Grandjean, Melendez and Sowton, 1964), and in a double-blind trial using 20 patients Srivastava, Dewar and Newall (1964) reported long-term propranolol showed "sufficient promise to justify a more extended trial." The results in our 16 patients with angina were disappointing, but it must be noted that they received 30 to 80 mg. daily whereas the present recommended dose of propranolol for this type of patient is 90 to 180 mg. per day. However two of our 16 patients developed hypotension at a dose level well below 80 mg. daily, and we believe that the higher doses should be approached with caution.

We have had little experience of the use of propranolol in other conditions. There is little doubt of the important place of beta blockade in the treatment of digitalis arrhythmias and to cover surgery in phaeochrome tumours. Propranolol may have a place in the diagnosis of these tumours (Paton, 1964) and in the treatment of hypertension (Prichard and Gillam, 1964). Other possible situations of which we have little personal experience include its use in hypertrophic obstructive cardiomyopathy, to potentiate the action of nor-adrenaline and metaraminol in the treatment of hypotension, and to reduce Parkinsonian tremor.

Pilkington, Lowe, Robinson and Titterington (1962) showed that the rise in plasma free fatty acids produced by adrenaline infusion was abolished by pronethalol but not by the alpha-receptor blocking agent phenoxybenzamine. Recently Muir, Chamberlain and Pedroe (1964) showed that in short-term experiments prone-

thalol caused a reduction in the mobilisation of non-esterified fatty acids and that the blood levels of non-esterified fatty acid fell during and after exercise. As this action of adrenaline on fatty acid release appeared to be a "beta" effect we investigated various lipid fractions in patients on long-term propranolol therapy. These patients were mostly suffering from ischaemic heart disease and no significant changes were seen in the lipid fractions measured. However a rise of free fatty acid was observed in three out of seven patients on long term treatment (over 2 months), including the only two cases on the drug for as long as nine months.

We did not find that patients on long-term propranolol developed abnormal transaminase levels as was reported by Tsolakas and others (1964). We agree with McNeill (1964) that propranolol should be given with caution in patients with bronchial asthma though it is not completely contraindicated. In addition long-term propranolol may be hazardous in patients with chronic bronchitis.

Production of a skin rash was one of the disadvantages of pronethalol (Alleyne and colleagues, 1963) but this was usually of an erythematous or urticarial type. Our two patients developed a slowly increasing irritation which in one case eventually developed into a fine scaly rash. In both cases the symptom improved immediately on withdrawing the drug and we believe that it was a true propranolol side-effect. Gastro-intestinal upset was another of the major drawbacks of treatment with pronethalol but not with propranolol, and we do not believe that propranolol was causative in the two patients who developed nausea in our series.

Propranolol-induced hypotension presents a serious drawback in the use of this drug in chronic ischaemic heart disease. When used, dosage increments of only 10 mg. weekly should be given and the blood pressure levels should be measured regularly. The drug should not be used in anginal patients with a low pressure.

Pronethalol is known to reduce cardiac output at rest (Dornhorst and Robinson, 1962) and was found to precipitate heart failure on occasions (Stock and Dale, 1963). Theoretically there is no reason why propranolol should not have the same effect although, as reported, we experienced little trouble from patients developing congestive heart failure.

Summary

Propranolol has been used in the treatment of a variety of conditions in 54 patients.

It was found to be of value in the reversion of supraventricular and ventricular tachycardia to sinus rhythm, but proved disappointing when given as prophylactic therapy to patients with paroxysmal arrhythmias. Similarly it proved ineffectual as a prophylactic drug to maintain sinus rhythm after DC shock reversion of atrial fibrillation.

Propranolol was effective in slowing the heart rate in both sinus tachycardia and atrial fibrillation and proved of benefit in patients with "effort syndrome."

In angina pectoris in a small uncontrolled series, results did not suggest that propranolol was of value.

In a further 50 patients given propranolol during anaesthesia it was found to be of value in abolishing ventricular arrhythmias and in slowing the heart rate in certain circumstances.

The dangers of propranolol are immediate hypotensive reactions following parenteral use, notably in shocked subjects, and delayed hypotensive responses when used as long-term oral therapy, especially in patients with ischaemic heart disease. Heart failure may theoretically be aggravated by the drug and bronchospasm has been observed in asthmatic and bronchitic subjects under treatment.

Addendum.—Since this paper was written, propranolol has been used with apparent benefit in the following situation: a patient developed ventricular fibrillation associated with an acute coronary occlusion and was successfully reverted to sinus rhythm using internal DC defibrillation. However return of ventricular fibrillation occurred twice in the following twenty minutes requiring further DC shock. Intravenous propranolol (2 mg.) was then administered and sinus rhythm was maintained and the patient survived.

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