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THE PROPERTIES OF BETA ADRENERGIC BLOCKING AGENTS

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THE current classification of adrenergic receptors is that described by Ahlquist (1948). He studied the effects of 6 sympathomimetic amines on a variety of effector systems, e.g. the heart, peripheral blood vessels, the uterus and the gastrointestinal tract. On the basis of his findings he suggested that there were two types of adrenergic receptor which he designated alpha and beta. The distribution of these receptors in different organs is given in Table 1 which also shows the responses produced by activation of these receptors. Receptors that when stimulated have an excitatory effect, e.g. constriction of blood vessels, were classified as alpha and those with an inhibitory effect on stimulation, e.g. relaxation of bronchial muscle were classified as beta. There was one main exception to this rule as the cardiac stimulation produced by sympathomimetic amines was attributed to stimulation of beta adrenergic receptors. Recently the relaxation of the gastrointestinal tract produced by catecholamines has been attributed to stimulation of both alpha and beta receptors (Ahlquist & Levy, 1959).

The effects on these receptors of some sympathomimetic amines used in therapeutics is shown in Table 2. The effects of a particular amine on an effector organ depends on the type of receptor with which it is capable of reacting and on the distribution of that receptor. Thus isoprenaline which stimulates only beta receptors increases heart rate and force and dilates the bronchi and the blood vessels in skeletal muscle.

Although adrenergic receptors have been classified pharmacologically, they have not been identified histologically or isolated biochemically. It

TABLE 1

Distribution and function of adrenergic receptors

Organ	Response to sympathetic stimulation	Receptor
Heart	Increase in heart rate	Beta
	Increase in cardiac contractility	Beta
Blood vessels	Constriction in skin and kidney	Alpha
	Dilatation in skeletal muscle	Beta
Eye	Dilatation of pupil	Alpha
Bronchi	Diiatation	Beta
Gastro-intestinal tract	Reduction in mortility	Alpha and beta

FIGRE 2

Drugs which stimulate adrenergic receptors

Drug	Receptor stimulated
Adrenaline	Alpha and beta
Noradrenaline	Alpha and beta
Isoprenaline	Beta
Orciprenaline	Beta
Phenylephrine	Alpha
Methoxamine	Alpha

has been suggested that the beta receptor is adenyl cyclase (Robinson, Butcher & Sutherland, 1966).

This classification of Ahlquist's has been vindicated by studies with drugs which block adrenergic receptors and thus prevent the action of drugs which stimulate the receptors. Drugs which block adrenergic alpha receptors have been used for many years. Dale (1906) first showed that extracts of ergot inhibited the vasconstrictor action of adrenaline and converted its pressor response to a depressor one by unmasking the dilatation of vessels in skeletal muscle. Other drugs which selectively block adrenergic alpha receptors but not beta receptors include dibenamine, phenoxybenzamine, tolazoline, thymoxamine and chlorpromazine.

The first drug which would selectively block adrenergic beta receptors was dichloroisoprenaline, which was described in 1958 (Powell & Slater, 1958). Several other drugs with a similar action have been described during this past 10 years. Some of these are listed in Table 3.

The one property which all these drugs possess is blockade of adrenergic beta receptors. Additional properties, which will be described in detail later, are possessed by some of them. Observations will be confined to the cardiovascular action of these drugs.

TABLE 3

Drugs which block adrenergic beta receptors

Dichloroisoprenaline (DCI)
Pronethalol (" Alderlin ")
Propranolol (" Inderal ")
I.C.I. 45763 (Kö 592)
MJ 1999 (" Sotalol ")
I.C.I. 50172 (practolol)
H 56/28—alprenolol (" Aptine ")
Ba 39098 (" Trasicor ")
Ro 3-3528

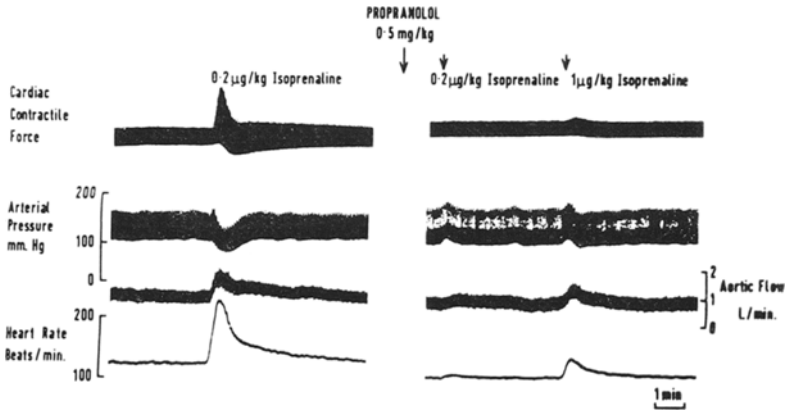

Fig. 1—Observations in dog anaesthetized with pentobaritone. Records of cardiac contractile force (right ventricle), femoral arterial pressure, ascending aortic flow and heart rate. Responses to the intravenous injection of isoprenaline before and after the intravenous injection of propranolol, 0.5 mg/Kg.

Adrenergic beta receptor blocking activity

The adrenergic blocking activity of these compounds can be readily investigated by studying their effects on the cardiovascular responses produced by the administration of isoprenaline (Shanks, 1966). The results of such an experiment are shown in Figure 1 which contains results from a dog anaesthetised with pentobarbitone and in which heart rate, arterial blood pressure and the force of contraction of the right ventricle were measured. The intravenous injection of isoprenaline increased heart rate and force and reduced arterial pressure due to stimulation of adrenergic beta receptors. When isoprenaline was again given after the administration of propranolol there was no change in any of these parameters.

Experiments of this type have been used to compare the activity of two or more drugs in blocking adrenergic beta receptors. The results of such an experiment are shown in Figure 2 in which the effects of the administration of increasing doses of propranolol and of its dextroisomer on the changes in heart rate, arterial diastolic pressure and cardiac contractile force are shown. As the dose of propranolol is increased there is a progressive reduction in the responses to isoprenaline. This experiment shows that propranolol is about 100 times more active than its dextro isomer in blocking adrenergic beta receptors.

Studies of this type are of value in demonstrating and comparing the effect of different compounds for blockade of adrenergic beta receptors. Of equal importance and of more practical and topical interest at present, is the assessment of the beta blocking activity of these compounds in man. If they are to be used in the treatment of disease it is necessary to determine the dose required in man to block the effects of increased activation of the beta receptors.

There are two main ways in which this can be done. In the first, the effects of the drug on the cardiovascular responses to the administration of isoprenaline are studied (Fig. 3). The intravenous infusion of the isoprenaline

increased heart rate and forearm blood flow but produced little change in arterial pressure. When isoprenaline was given for a second time after the intravenous infusion of 1 mg. propranolol, its effects were greatly reduced. Figure 3 also shows the effects of propranolol on the cardiovascular effects of adrenaline. After propranolol adrenaline reduced heart rate and forearm blood flow but produced a greater increase in arterial pressure. The bradycardia occurs as a reflex response to the increase in arterial pressure which follows the unmasking of the peripheral vasoconstrictor action of adrenaline after propranolol has blocked its vasodilator action. Studies of this type have been carried out in man to show the adrenergic beta receptor blocking activity of pronethalol (Dornhorst & Robinson, 1962), propranolol (Black, Crowther, Shanks, Smith & Dornhorst, 1964), I.C.I. 45763 (Shanks, Wood, Dornhorst & Clark, 1966), MJ 1999 (Frankl & Soloff, 1968). Comparative studies have been made with H56/28 (alprenolol) and propranolol (Johnsson, Norrby & Solvell, 1967), I.C.I. 50172 and propranolol (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968) and propranolol and its dextro isomer (Brick, Hutchison & Roddie, 1969). A comparison of the effects on an isoprenaline tachycardia of the oral administration of H56/28 and propranolol has been carried out by Ablad, Johnsson, Norrby & Solvell (1967) and of Ro 3-3528 and propranolol by Hill & Turner (1968). Hill and Turner (1968) administered the isoprenaline to their subjects by inhal-

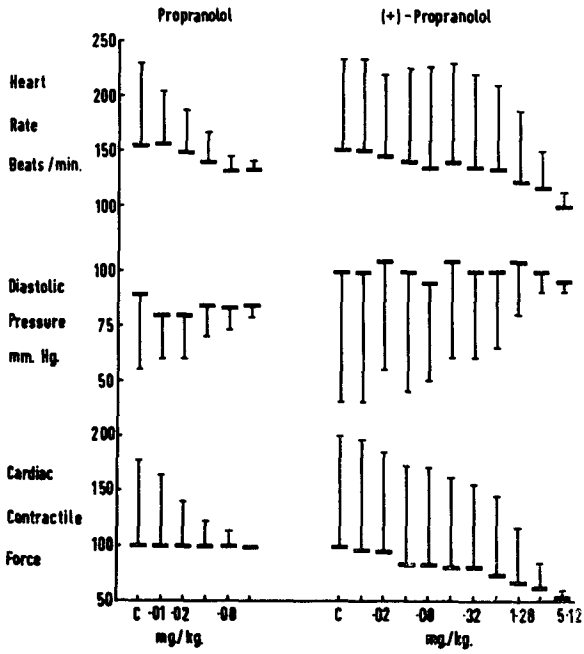

Fig. 2—Observations in dogs anaesthetized with thialbarbitone andchloralose. Heart rate, beats/min., femoral diastolic arterial pressure, mm Hg., and right venticular contractile force, expressed as percentage of initial control value, were recorded. Resting level of each parameter is represented by (▬) and the maximum response to isoprenaline (0.4 ug/Kg) by (—). The effect of increasing doses of propranolol and (+) — propranolol on resting levels and on the responses to isoprenaline are shown; averaged results from three and two dogs respectively.

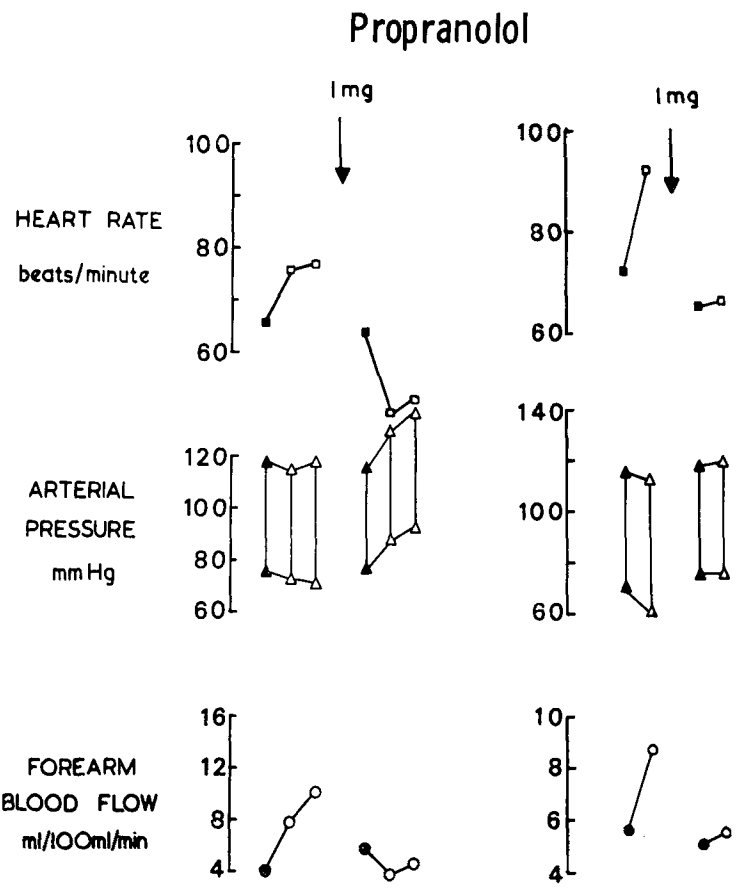

Fig. 3—Right hand panel : mean results from four subjects in which responses to the intravenous infusion of isoprenaline at 3 ug/min for 3 minutes were recorded before and after propranolol 1 mg.

Left hand panel : mean results from three subjects in which responses to the intravenous infusion of adrenaline at 5 and 10 ug/min for 3 minutes were recorded before and after propranolol 1 mg.

Solid symbols denote resting levels and the open symbols denote the effect of isoprenaline or adrenaline infusion.

ation using the method described by Chamberlain (1967). The effects of isoprenaline on heart rate are the same on administration by inhalation or by intravenous infusion except that a much smaller dose is required for the latter method (Patterson, Conolly, Davies & Dollery, 1968.

The second and more physiological way to assess the activity of an adrenergic beta receptor blocking compound in man is to investigate its effect on the increase in heart rate that occurs during severe exercise in healthy subjects. The increase in heart rate produced by exercise results from a reduction in parasympathetic activity to the heart and an increase in sympathetic activity (Robinson, Epstein, Beiser & Braunwald, 1966; Chamberlain, Turner & Sneddon, 1967). The former predominates at low work loads and the latter at high work loads with the heart rate during exercise reach-

ing 160-170 beats/min. Thus when the effects of a drug are being studied on the sympathetic component of an exercise tachycardia, is is essential that strenuous exercise which will increase heart rate above 150 beats/minute be used.

The effects on an exercise tachycardia of a single dose of an adrenergic beta receptor blocking agent given by intravenous injection or orally has been described in many reports, e.g. pronethalol (Bishop & Segal, 1963; Chamberlain & Howard, 1964; Schroder & Werko, 1964); propranolol (Epstein, Robinson, Kahler & Braunwald, 1965; Shinebourne, Fleming & Hamer, 1967); I.C.I. 45763 (Shanks *et al.*, 1966) and I.C.I. 50172 (Brick *et al.*, 1968). In all cases the exercise tachycardia was markedly reduced by the beta blocking agent (Figure 4).

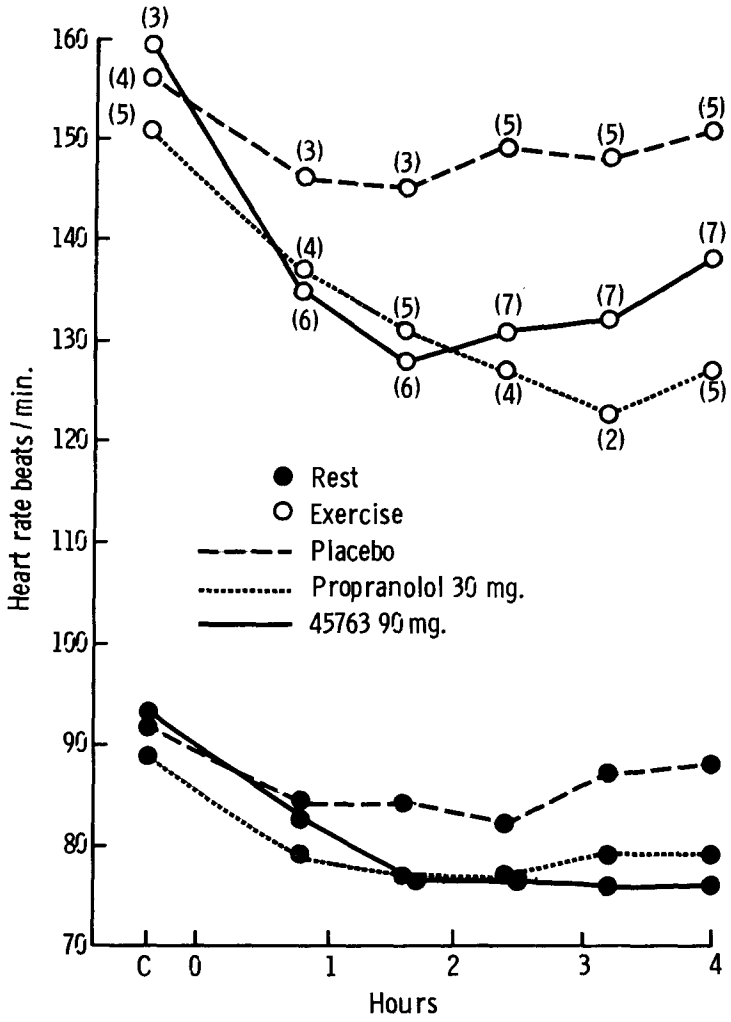

Fig. 4—The effect of I.C.I. 45763, 90 mg (——), propranolol, 30 mg. (·····) and placebo (----) on resting heart rate (●) and exercise tachycardia (o) administered orally at time 0. Averaged results from nine subjects; the standard error of the mean is given in brackets.

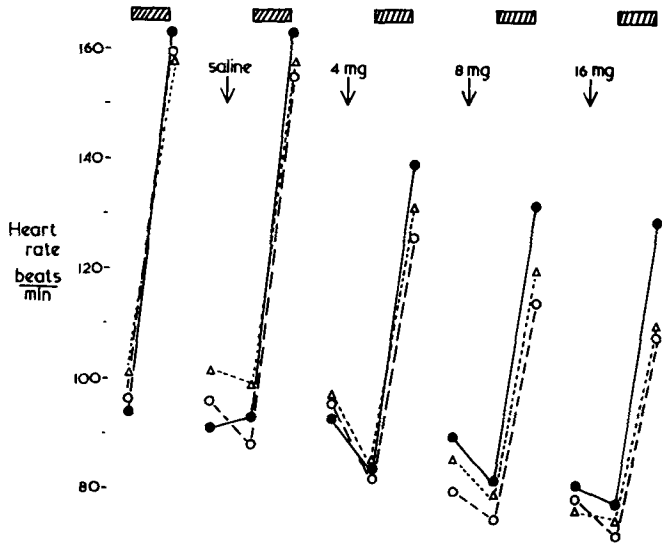

Fig. 5—Comparison of the effects of the intravenous injection of saline and of three doses of I.C.I. 50172 (●—●), propranolol (o---o) and I.C.I. 45763 (Δ---Δ) on heart rate at rest and at the end of a 3 min. period of excercise (|////|). Mean of observations in five subjects who received each drug on separate occasions. The left-hand set of responses were obtained during a control run.

However, few studies have been carried out to determine the minimum dose of any particular drug required to produce the maximum reduction in the exercise tachycardia. As one of the main indications for the use of these drugs is in angina of effort in which these drugs probably act by reducing the increase in sympathetic activity to the heart during exercise, it is surprising that studies of this type are not more numerous. The only study of the effects of the oral administration of increasing doses of propranolol on the increase in heart rate during exercise has been carried out by Chamberlain (1967). He showed that at least 70 mg. propranolol orally in a single dose was required to produce maximal reduction in the exercise tachycardia. A similar reduction in the tachycardia was obtained by cardiac sympathectomy and propranolol. The effect of the intravenous injection of a series of increasing doses of three adrenergic beta receptor blocking drugs on an exercise tachycardia has recently been described (Brick *et al.*, 1968). The results are shown in Figure 5. These indicate that at least 16 mg. propranolol is required to produce maximum reduction in the tachycardia. The dose of an adrenergic beta receptor blocking agent to be used in angina of effort, should be that which produces maximum reduction in an exercise tachycardia. These studies suggest that it should be at least 60-70 mg. orally four times per day to maintain a constant blood level of the drug. Variation in the dose that produces maximal blockade may occur as a result of individual variation in rates of absorption, metabolism, excretion and in blocking beta receptors (Gillam & Prichard, 1966).

It is essential that studies of this type are carried out using both intra-

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venous and oral administration of the drug so that its adrenergic beta receptor blocking activity can be determined and compared with that of existing drugs. These studies must take place before the commencement of clinical trials so that these are carried out with the appropriate dose of the drug.

One of the effects of the absence of studies of this type was shown with verapamil ("Cordilox") which was introduced 18 months ago as a mild beta adrenergic blocking compound for the treatment of angina (Bateman, 1967). Studies in animals showed that it reduced the effect of isoprenaline on the heart but only when given in doses which produced marked cardiac depression; its effect was comparable to that of pentobarbitone (Benfey, Greeff & Hegg, 1967). After the introduction of verapamil we compared the effects of it and of propranolol on oral administration on the increases in heart rate produced by the intravenous infusion of isoprenaline and by severe exercise (Grant, McDevitt & Shanks, 1968). Propranolol abolished the isoprenaline tachycardia and reduced the increase in heart rate on exercise but verapamil was without effect on both responses. These results indicate that verapamil does not block adrenergic beta receptors in man and hence the effects of the sympathetic nervous system on the heart as has been claimed (Bateman, 1967).

At an early stage in the development of propranolol, a controlled trial was carried out in angina of effort using a dose of 20 mg. three times daily. The drug produced no improvement (Srivastava, Dewar & Newell, 1964). Many subsequent studies with larger doses have shown that propranolol is extremely effective in the treatment of angina. Later investigations have shown that the dose of propranolol required to reduce maximally an exercise tachycardia is in the region of 50-80 mg. in a single dose. In retrospect such studies should have been completed before beginning controlled studies with a fixed dose of the drug in angina.

Selective blockade of adrenergic beta receptors

Propranolol, pronethalol, I.C.I. 45763, MJ 1999, alprenolol and related drugs block all adrenergic beta receptors (Shanks, 1966). I.C.I. 50172, on the other hand, only blocks adrenergic beta receptors in the heart but not in the peripheral blood vessels or in the trachea and bronchi (Dunlop & Shanks, 1968). The effect of I.C.I. 50172 on the cardiovascular responses to isoprenaline in an anaesthetized dog are shown in Figure 6. I.C.I. 50172 blocked the increases in heart rate and force but not the fall in diastolic pressure produced by isoprenaline; propranolol blocked all three responses. Further experiments showed that I.C.I. 50172 abolished cardiac arrhythmias produced by adrenaline, and that it had little effect on the bronchodilator action of isoprenaline. This selective blockade of beta receptors in the heart by I.C.I. 50172 has been more difficult to demonstrate in man. In normal subjects the intravenous infusion of I.C.I. 50172 in doses up to 20 mg. had no significant effect on the increases in heart rate produced by isoprenaline or by adrenaline but significantly reduced the increases in heart rate produced by severe exercise (Fig. 5) and by tilting (Brick *et al.*, 1968). It is not clear why I.C.I. 50172 failed to block the isoprenaline tachycardia yet blocked effectively the sympathetic component of the tachycardias of exercise and tilting. The peripheral vasodilator action of isoprenaline was

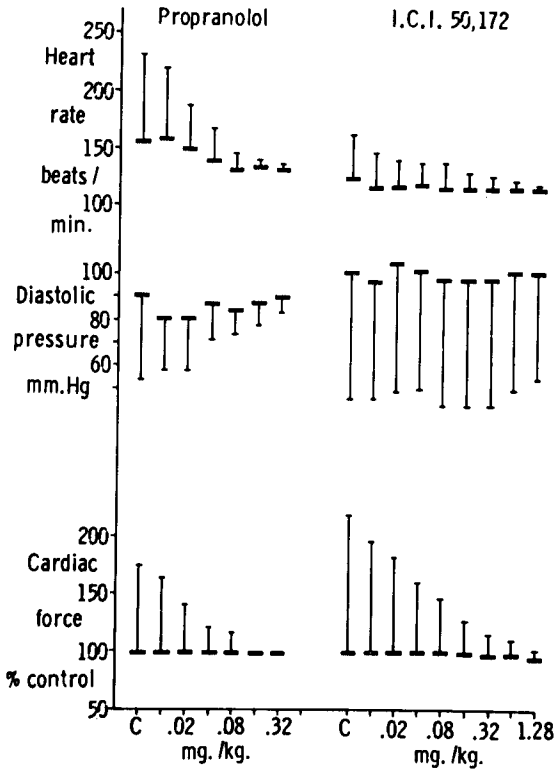

Fig. 6—Observations in dogs anaesthetized with thialbarbitone and chloralose. Changes in heart rate, cardiac contractile force (expressed as percentage of initial resting value) and arterial diastolic pressure produced by the intravenous injection of isoprenaline (2.0 ug/Kg) before and after increasing doses of I.C.I. 50172 and propranolol. Mean of observations in three dogs for each drug. Symbols as in Figure 2.

not reduced by I.C.I. 50172. Recently Harrison and Turner (1969) have shown that the oral administration of I.C.I. 50172 reduced the increase in heart rate but not the peripheral vasodilatation produced by isoprenaline.

The intravenous administration of propranolol in asthmatic patients increases airways resistance and often produces dyspnoea and wheeze as a result of blockade of tonic sympathetic drive to adrenergic beta receptors in the bronchi (McNeill & Ingram, 1966). A comparison of the effects of propranolol and I.C.I. 50172 in asthmatic patients showed that the latter drug did not increase airways resistance (Macdonald & McNeill, 1968). These results suggest that in man I.C.I. 50172 produces selective blockade of adrenergic beta receptors in the heart and indicate that it may safely be given to patients with obstructive airways disease.

Intrinsic Sympathomimetic activity

Dichloroisoprenaline, the first adrenergic beta receptor blocking compound to be described, although blocking adrenergic beta receptors also stimulated them so that it increased heart rate and force (Powell & Slater, 1958; Moran & Perkins, 1958). This has been termed "intrinsic sympatho-

mimetic activity" by Dresel (1960). In man the infusion of a large dose of dichloroisoprenaline into the brachial artery was followed by a tachycardia and palpitations (Glover, Greenfield & Shanks, 1962). This sympathomimetic action made dichloroisoprenaline unsuitable for clinical investigation. Pronethalol did not possess the intrinsic sympathomimetic activity of dichloroisoprenaline although it blocked adrenergic beta receptors (Black & Stevenson, 1962). It reduced slightly heart rate and force in anaesthetized animals. This was attributed to the blockade by pronethalol of tonic sympathetic activity to the heart (Black & Stevenson, 1962). In man pronethalol reduced resting heart rate but increased or had no effect on stroke volume (Bishop & Segal, 1964; Chamberlain & Howard, 1964; Schröder & Werko, 1964). After the discovery of propranolol, studies in animals showed that it produced a greater reduction in heart rate and heart force than pronethalol (Black, Duncan & Shanks, 1965). In animals pretreated with syrosingopine to deplete the stores of noradrenaline in the heart and thus abolish sympathetic drive, propranolol produced no change in heart rate but it was increased by pronethalol. Consequently it was suggested that pronethalol possessed slight intrinsic sympathomimetic activity so that although it blocked adrenergic beta receptors in the heart, the resultant inhibition of sympathetic drive to the heart reducing heart rate was compensated for by a small degree of stimulation of beta receptors by pronethalol so that heart rate did not change (Black *et al.*, 1965). A comparison of the effects of pronethalol and propranolol on cardiac dynamics in man has not been made but from a survey of the separate studies of the two drugs which have been made, it would appear that their effects are different. The intravenous injection of propranolol in normal people at rest reduces heart rate and stroke volume significantly (Epstein *et al.*, 1965; Harris, Schoenfeld, Brooks & Weissler, 1966; Sowton & Hamer, 1966). If it is assumed that the effects of propranolol result entirely from the removal of resting sympathetic drive to the heart, the absence of an effect of pronethalol on stroke volume may indicate that in man it has a positive inotropic effect.

Recently several new adrenergic beta receptor blocking agents which have slight intrinsic sympathomimetic activity in animals have been described. These include I.C.I. 45763, alprenolol (H56/28), Ba 39098 (Trasicor-Ciba) and I.C.I. 50172. The intravenous injection of I.C.I. 50172 (5-25 mg.) in man at rest or during continuous exercise reduced heart rate without changing cardiac output (Gibson & Sowton, 1968; Sowton, Balcon, Cross & Frick, 1968). No comparison was made with propranolol. The effects of *equipotent* beta blocking doses of alprenolol and propranolol have been compared in 5 healthy subjects (Forsberg & Johnsson, 1967). Propranolol reduced heart rate and cardiac output significantly whereas alprenolol had no effect on these functions. These results suggest that although alprenolol and I.C.I. 50172 block adrenergic beta receptors in man, they may also have a positive inotropic action.

The administration of propranolol to patients with latent or overt cardiac failure worsens their condition (Stephen, 1966). This has been attributed to the removal of sympathetic drive to the heart which is required for the maintenance of compensation in these patients. It has been suggested that adrenergic beta receptor blocking agents which have an intrin-

sic sympathomimetic action may not depress ventricular function further in patients in which it is impaired (Linko, Süttonen & Ruosteenoja, 1967). Gibson, Balcon & Sowton (1968) have used I.C.I. 50172 in 8 patients with severe congestive cardiac failure and in 11 patients shortly after valve replacement. Each patient had a rapid ventricular rate which was not controlled with other therapy. I.C.I. 50172 reduced the ventricular rate in all but two patients without producing significant side effects, e.g. bradycardia or aggravation of heart failure.

These investigators suggested that propranolol was contraindicated in these patients owing to the risk of severe depression of left ventricular function. Ideally, a comparison should be made between the effects of I.C.I. 50172 and propranolol in the same patients to determine if I.C.I. 50172 is superior in the treatment of arrhythmias in patients with cardiac decompensation. At present the effects of propranolol on these arrhythmias, i.e. rapid atrial fibrillation and ventricular tachycardias in patients already treated with adequate doses of digitalis, are not well documented. Rowlands, Howitt and Markman (1965) describe a patient in congestive heart failure with atrial fibrillation and a rapid ventricular rate treated with digoxin and diuretics with little effect. The congestive heart failure cleared completely after starting treatment with propranolol to reduce the ventricular rate. It is possible that propranolol may have had a similar effect to I.C.I. 50172 in the patients treated by Gibson *et al.*, 1968, as the beneficial effect was obtained by reducing ventricular rate. It should be remembered that Stock and Dale (1963) first described cardiac failure occurring during therapy with pronethalol, which it is now known possesses intrinsic sympathomimetic activity similar to that of I.C.I. 50172 and other related drugs. This suggests that intrinsic sympathomimetic activity may not protect against the development of heart failure due to blockade of beta receptors.

It would appear that investigations comparing the effects of adrenergic beta receptor blocking drugs, with and without intrinsic sympathemimetic activity, are required in patients in whom cardiac function is impaired to determine if sympathomimetic activity has a beneficial effect.

Local anaesthetic or quinidine-like activity

Shortly after Stock and Dale (1963) showed that pronethalol was effective in the treatment of various cardiac arrhythmias, Morales-Aguilera and Vaughan Williams (1965) demonstrated in animals that it had a quinidine-like effect on the heart and that it was a potent local anaesthetic. Since, there has been much controversy over the contribution the quinidine-like or local anaesthetic action makes to the effect of adrenergic beta receptor blocking agents in angina of effort and in cardiac arrhythmias in man.

The terms quinidine-like and local anaesthetic actions are two terms to describe the same effect of the drug on cell membranes of the heart and nerve fibre respectivly which results from the inhibition of the transfer of sodium across the membrane (Vaughan Williams, 1966). In anaesthetised guinea-pigs, pronethalol reduced the toxicity on the heart of ouabain (Sekiya & Vaughan Williams, 1963). Subsequently Lucchesi (1965) showed that pronethalol and its dextroisomer, which has little beta blocking activity, were equally effective in abolishing ouabain induced arrhythmias in dogs,

TABLE 4

The properties of propranolol and its isomers

The activity of propranolol is taken as 1

Drug	Beta blockade	Local anaesthetic	Adrenaline arrhythmias	Ouabain arrhythmias
Racemic propranolol	1	1	1	1
Laevo isomer	2	1	2	2
Dextro isomer	.02	1	.02	1

whereas racemic pronethalol was much more effective than the dextro isomer in inhibiting adrenaline induced arrhythmias.

Similar observations have now been made with propranolol and its dextro and laevo isomers (Howe & Shanks, 1966; Lucchesi, Whitsitt & Stickney, 1967; Barrett & Cullum, 1968). The activity of propranolol and its two isomers for their activity in blocking adrenergic beta receptors in the heart, local anaesthetic activity on a frog sciatic nerve preparation, activity in preventing arrhythmias following the injection of adrenaline in cats sensitised with halothame and activity in abolishing ouabain induced arrhythmias in dogs, is summarised in Table 4. These results indicate that there are two ways in which propranolol can abolish cardiac arrhythmias (Figs. 7 and 8). The first is due to blocade of adrenergic beta receptors and oc-

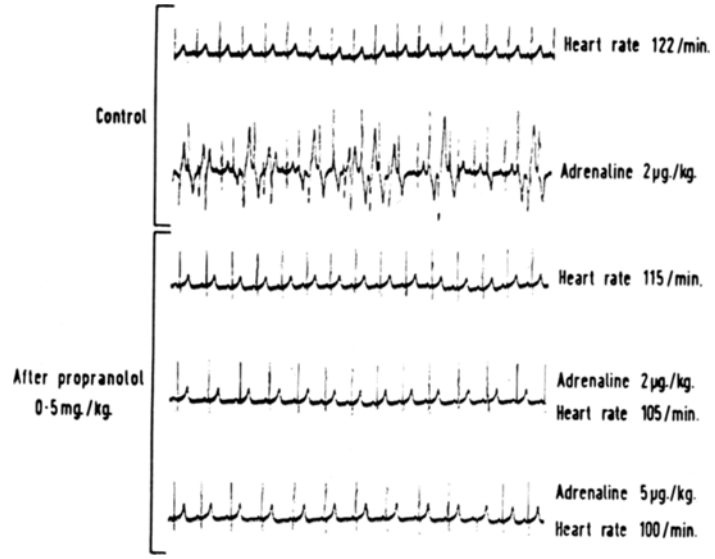

Fig. 7—The electrocardiogram (Lead 2) in a cat anaesthetized with chloralose and breathing halothane, 1%. The records from above downwards are : control; 10 seconds after the intravenous injection of adrenaline, 2 ug/Kg; 5 minutes after the intravenous injection of propranolol, 0.5 mg/Kg; 10 seconds after the intravenous injection of adrenaline, 2 ug/Kg; 10 seconds after adrenaline, 5ug/Kg. Propranolol protected against the adrenaline arrhythmias.

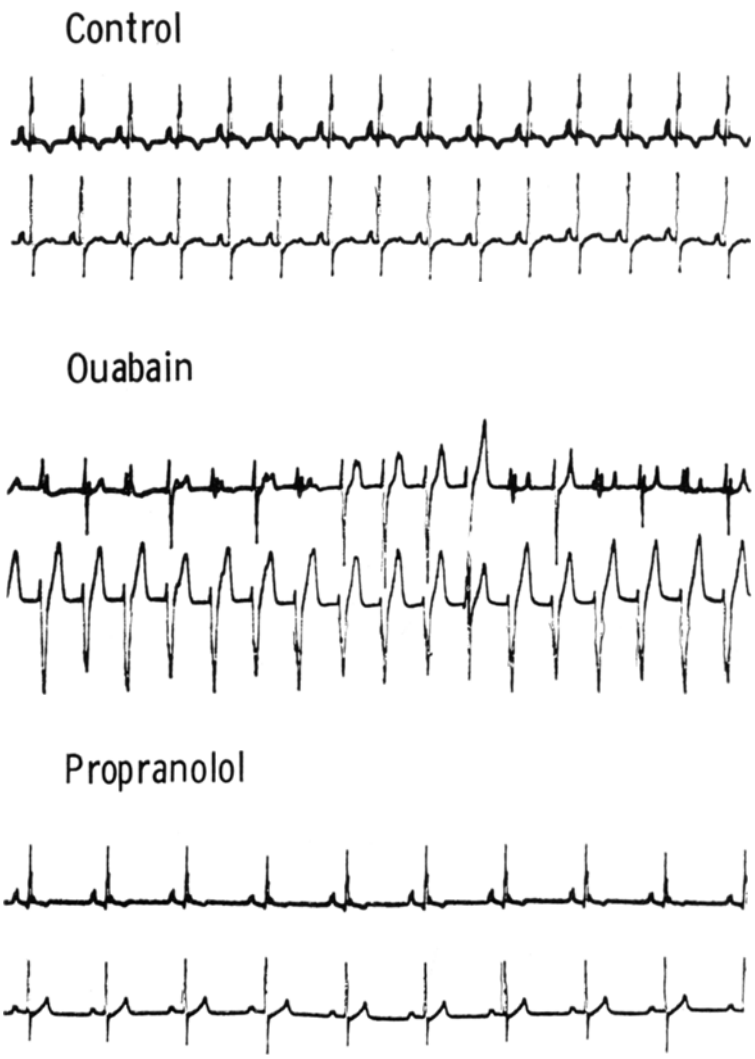

Fig. 8—Observations in dog anaesthetized with pentobarbitone. Electrocardiograms (Leads 1 and 2) obtained before (upper 2 records) and after (middle 2 records) the intravenous injection of outbain, 100 ug/Kg. After establishment of the arrhythmia propranolol was infused intravenously at 1 mg/Kg/min. until sinus rhythm returned (lower 2 records). The arrhythmia was abolished by 5 mg/Kg propranolol.

curs in arrhythmias in which there is an adrenergic trigger (Shanks & Dunlop, 1967). The second is due to the local anaesthetic action which appears to be responsible for the effect of these agents on ouabain induced arrhythmias; it should be noted that a much larger dose of the drug is necessary for this effect. Studies with other adrenergic beta receptor blocking drugs confirm this interpretation. Thus H56/28 (alprenolol) and its dextro isomer, which are local anaesthetics, are equally effective in abolishing ouabain induced arrhythmias (Duce, Garberg & Johansson, 1967). On the other hand, MJ 1999 and I.C.I. 50172 which have no local anaesthetic activity

have no effect on ouabain induced arrhythmias but are extremely effective in preventing adrenaline induced arrhythmias (Somani, Fleming, Chan & Lum, 1966; Dunlop & Shanks, 1968).

It has been suggested that the local anaesthetic property of propranolol may contribute or be responsible for its effect in angina of effort and in various cardiac arrhythmias in man.

After the administration of propranolol, the increases in heart rate, cardiac output and cardiac work during exercise are reduced without reducing the amount of physical work performed (Epstein *et al.*, 1965; Shinebourne *et al.*, 1967. Thus in patients with angina of effort propranolol probably increases the effort tolerance by reducing the cardiac work performed for a given amount of external physical work. The dose of propranolol required for a maximum therapeutic effect in angina is in the region of 40-100 mg. four times daily (Gillam & Prichard, 1966). It has been assumed that this dose is greater than that required to block adrenergic beta receptors and consequently suggested that propranolol must have other actions which contribute to its beneficial effect, e.g. its quinidine-like myocardial depressant action (B.M.J. 1969 a). However, it has been shown that at least 70 mg. propranolol by mouth is required to produce marked blockade of the increase in sympathetic drive to the heart during exercise (Chamberlain, 1967). This dose is similar to that used in the treatment of angina. From a detailed analysis of many studies with propranolol, Barrett (1969) has shown that the dose of propranolol which produced a beneficial effect on oral or intravenous administration in angina of effort was similar to that required for blockade of adrenergic beta receptors as judged by inhibition of an isoprenaline tachycardia or by a maximum reduction in an exercise tachycardia. In animals the quinidine-like action of propranolol is only observed at doses of 20-30 times greater than that required to block adrenergic beta receptors in the heart (Howe & Shanks, 1966; Lucchesi *et al.*, 1967; Flacke Osgood & Bendixen, 1967; Parmley & Braunwald, 1967; Barrett & Cullum, 1968). As the dose of propranolol used in the treatment of angina in man is only that which blocks adrenergic beta receptors in the heart, it appears most unlikely that this dose will exert any quinidine-like action on the heart. The contribution of the quinidine-like action of adrenergic beta receptor blocking agents to their beneficial effect in angina has been analysed by Bjorntorp (1968) who has compared the effects of H56/28 racemate against a placebo and against the dextro isomer of H56/28 in controlled trials using 100 mg. of each drug four times per day. The dextro isomer had no effect on the number of attacks of angina whereas the racemate produced a significant reduction when compared with the placebo. The two drugs have the same local anaesthetic action but the racemate is 50 times more potent in blocking beta receptors (Ablad *et al.*, 1967 a & b).

All these studies suggest that the beneficial effect of adrenergic beta receptor blocking agents in angina results from blackade of adrenergic beta receptors in the heart.

Pronethalol, and latterly propranolol and alprenolol (H56/28) have been shown to be of value in controlling various types of cardiac arrhythmias including sinus tachycardia; atrial flutter and atrial fibrillation, through slowing of the ventricular rate, arrhythmias arising from digitalis intoxica-

tion and to a lesser extent supraventricular and ventricular ectopic beats (Stock & Dale, 1963; Epstein & Braunwald, 1966; Linko *et al.*, 1967).

There is still controversy over the mode of action of these drugs in arrhythmias (B.M.J. 1969 b). Propranolol reduces the height and rate of rise of the action potential, prolongs the effective refractory period and has an anti-fibrillatory effect on atrial muscle (Vaughan Williams, 1966). Similar effects are produced by procaineamide and quinidine (Morales-Aguilera & Vaughan Williams, 1965). It is not clear if these effects of propranolol are due entirely to its beta blocking activity or to its local anaesthetic action or to a combination of both as the doses of propranolol used in these studies were much greater than would be required to block beta receptors. Propranolol and its dextro isomer are equally effective in prolonging the refractory period and depressing the rate and force of cardiac contraction in isolated tissues but in doses much greater than those for blockade of beta receptors (Levy & Richards, 1966; Parmley & Braunwald, 1967). This property of propranolol and its dextro isomer is probably responsible for their action in abolishing ouabain induced arrhythmias in animals as shown in Figure 8 (Howe & Shanks, 1966; Lucchesi *et al.*, 1967). For this effect *2-4 mg/Kg* of each drug was required which is greatly in excess of that required to block beta receptors and to abolish arrhythmias produced by adrenaline—see Figure 7 (Dunlop & Shanks, 1967; Barrett & Cullum, 1968). In man propranolol when effective in controlling arrhythmias does so in doses comparable to or less than that required for beta blockade.

In an effort to elucidate the mode of action of propranolol in patients with cardiac arrhythmias, the effects of propranolol and its dextro isomer have been compared on various cardiac arrhythmias (Howitt, Husaini, Rowlands, Logan, Shanks & Evans, 1968). The dextro isomer had less effect on sinus rate and atrial flutter and fibrillation when given in the same dose as racemic propranolol. Both drugs were either ineffective or equally effective in supraventricular and ventricular ectopic beats. Small doses (5 mg.) of the dextro isomer were effective against arrhythmias due to digitalis intoxication; racemic propranolol had the same effect. These results suggest that the effect of propranolol in most arrhythmias is due to its beta blocking action and that another mechanism may be responsible for its effect in other arrhythmias. This mechanism may not be its local anaesthetic action as the effective dose in man was always less than that required for beta blockade. These conclusions have been supported by the study of Gibson *et al.*, (1968) who found that I.C.I. 50172 which has no local anaesthetic action was effective in controlling the ventricular rate in 7 out of 8 patients with atrial fibrillation and in 6 out of 9 patients with supraventricular tachycardia. Further studies will be required to compare the effects of propranolol and I.C.I. 50172 in other types of cardiac arrhythmias. These investigations may indicate that some arrhythmias may respond to blockade of adrenergic beta receptors while others may only be controlled by a drug possessing a quinidine-like effect.

Summary

Observations in animals now indicate that adrenergic beta receptor blocking agents may possess in addition intrinsic sympathomimetic activity and a local anaesthetic action. Unlike other beta receptor blocking agents I.C.I. 50172 selectively blocks only the receptors in the heart. The role

of these different properties in the beneficial effect these drugs is not yet clearly understood. Further studies comparing the effects of drugs with different properties in angina and cardiac arrhythmias are required. Such studies must be carried out with equivalent beta receptor blocking doses of the drugs.

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