A review of beta-blockers and their use in general practice

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For over ten years propranolol (' Inderal ') and practolol (' Eraldin ') have been the only two beta-adrenergic blocking agents (β-blockers) available for clinical use, but more recently many more similar drugs have been developed so that at present there are nine β-blockers (eight iu the United Kingdom) available to practitioners.

Beta-adrenergic receptors are found scattered throughout the body and for practical purposes are divided into those located in the heart (β^1-receptors), and those found at the periphery, particularly the bronchi and peripheral blood vessels (β^2-receptors). Beta-blockade will therefore antagonise the pharmacological stimulatory effect of the catecholamines at these sites and it is through this activity that the β-adrenergic blocking agents have been promoted in therapeutics.

However, in addition to β-blockade, these drugs have been found to have other pharmacological properties which suggests the possibility in the future of many other therapeutic uses.

Properties of the beta-blocking agents,

The following are the main pharmacological actions of β-blocking drugs:,

(1) They reduce the heart rate (negative chronotropic effect)*,

(2) They reduce the force of contraction of the heart muscle (negative inotropic effect)*,

(3) They increase bronchoconstriction**,

(4) They cause peripheral vasoconstriction especially of the skeletal blood vessels**,

(5) Some have a membrane stabilising action (also known as a local anaesthetic or quinidine-like action),

(6) Some have an intrinsic sympathomimetic action of their own,

(7) Some reduce plasma renin and angiotensin*,

(8) Some reduce the release of free fatty acids from fat stores*,

(9) Some reduce hepatic gluconeogenesis causing hypoglycaemia,

(10) Some reduce the release of insulin from the pancreas**,

(11) Some act on the central nervous system.

*refers to blockade of β_1-receptors

**refers to blockade of β_2-receptors

As all the agents have different chemical structures it follows that they also differ, if only marginally, in their pharmacological properties so that the above actions occur with each to a differing degree. The comparative actions of the different known β-blockers are summarised in table 1.

By far the most important practical pharmacological actions lie in blocking the β^1-receptors in the heart, and it is for this reason that these agents have been developed in recent years for use in the treatment of angina pectoris and hypertension.

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TABLE 1
THE COMPARATIVE PROPERTIES OF THE BETA-BLOCKERS

Beta-blocker	*Blocks β_1 receptors*	*Blocks β_2 receptors*	*Local** anaesthetic effect*	*Sympathomimetic effect*	*Reduces plasma renin*	*Reduces plasma lipids*	*Reduces insulin release*	*Plasma half life*
ACEBUTOLOL 'Sectral'	+	weak	+	weak	ND	ND	ND	4–5 hours
METOPROLOL 'Betaloc' 'Lopressor'	+	−	weak	−	+	+	+	3–4 hours
OXPRENOLOL 'Trasicor'	+	+	+	+	+	+	+	ND
PINDOLOL 'Visken'	+	+	weak	+	−	−	weak	3–4 hours
PRACTOLOL* 'Eraldin'	+	−	−	+	−	−	−	10–15 hours
PROPRANOLOL 'Inderal'	+	+	+	−	+	+	+	3 hours
SOTOLOL 'Betacardone' 'Sotocor'	+	+	−	−	+	ND	+	10–16 hours
TIMOLOL 'Blocadren'	+	+	−	−	+	ND	+	ND
ATENOLOL 'Tenormin'	+	−	−	−	ND	ND	ND	ND
TOLAMOLOL	+	−	ND	—	+	+	+	ND

ND: not documented

**Local anaesthetic action (membrane stabilising or quinidine-like action)

*Practolol was withdrawn from use by general practitioners in 1975 because of reported side-effects.

Hypertension

It is not yet clear how β-blockers reduce blood pressure, but the following factors may be implicated:

(1) *β_1-receptor blockade*

The main effect of blocking the β_1-receptors in the heart is to reduce the heart rate and force of contraction of the myocardial fibres. These effects lead to a lowering of cardiac output in the short term (Johnsson *et al.*, 1969) and perhaps in the long term either through adaptive changes (Tarazi *et al.*, 1972) or possibly via the re-setting of the baroreceptors to a lower level (Prichard and Gillam, 1969).

(2) *Reduction of plasma renin*

Many β-blockers lower plasma renin levels in both normal and hypertensive people (Michelakis and McAllister, 1972). Although there is some evidence to suggest that hypertensive patients with elevated plasma renin respond better to treatment with β-blockers than those with normal

plasma renin levels (Buhler *et al.*, 1972). Morgan (1975) has shown that the lowering of plasma renin with pindolol did not correlate with the reduction of blood pressure, and Stokes *et al.* (1974) showed that the antihypertensive effect of propranolol correlated poorly with its effect on plasma renin activity. It is, therefore, uncertain whether the property of reducing plasma renin is important in the hypotensive effect of the β-blockers.

(3) *Effect on the systematic circulation*

There is some evidence to suggest that β-blockers reduce the plasma volume (Julius *et al.*, 1972) and a reduction in venous return (Krauss *et al.*, 1972). Although this could occur from the reduction of plasma renin, it is obviously not the only factor involved as a single dose of propranolol, insufficient to lower plasma renin, is enough to reduce the plasma volume (Julius *et al.*, 1972).

(4) *Effect on the central nervous system*

It may be that the β-blocking agents exert some C.N.S. effect in the reduction of blood pressure since there is indirect evidence that these drugs enter the nervous system as indicated by clinical side-effects such as insomnia, dreams, and depression seen in some patients taking β-blockers (Greenblatt and Shader, 1972).

(5) *Membrane stabilising effect*

The relevance of the membrane stabilising or local anaesthetic effect of the β-blockers in terms of reducing blood pressure is unclear at present. Indeed the merit of this property now even seems to be in doubt, as recent evidence suggests that in large doses the membrane stabilising action can delay cardiac conduction (Roy *et al.*, 1975).

Choice of beta-blocker in treating hypertension

Although many trials have been conducted using the various different agents available, none has been designed to compare all the currently available β-blockers on the same basis, and it still remains unclear which, if any, are more effective in lowering blood pressure.

Propranolol, oxprenolol, alprenolol, pindolol and sotolol are about equally effective in lowering blood pressure (Waal-Manning, 1970), whereas practolol is rather less effective (Prichard *et al.*, 1971). Indeed practolol is not promoted for use in hypertension other than in those patients thought to be at risk of developing asthma. The fact that some people have used these agents in very high doses in their trials whilst others have used far smaller doses indicates that there is still much work to be done to achieve the optimum dosage scale for each β-blocker in the treatment of hypertension.

Selecting hypertensive patients for treatment with beta-blockers

Although all hypertensive patients should benefit from treatment with one of these drugs, the following should theoretically gain special help from their use:

(1) Patients with hypertension accompanied by:

(a) Angina,
(b) Cardiac dysrhythmias,
(c) Migraine,
(d) Concurrent tricyclic antidepressant therapy.

(2) Patients with signs of excessive β-adrenergic activity, especially anxiety, tension, and tachycardia.

(3) Patients who develop the unpleasant symptoms of postural hypotension when taking other types of hypotensive drug. The β-blockers have very little, if any, postural hypotensive effect.

(4) Patients who are taking large doses of other types of hypotensive drug. The addition of a β-blockers will allow the dose of these other drugs to be reduced. In this respect the β-blockers are especially effective when used in combination with the thiazide diuretics, alpha methyl dopa, guanethidine, reserpine, clonidine, and hydrallazine.

(5) Men who develop impotence when taking some of the other antihypertensive drugs, particularly alpha methyldopa.

(6) Patients with raised plasma renin levels.

Angina pectoris

In comparison with hypertension, it is a little clearer how the β-blockers work in the reduction of both the frequency and the severity of attacks of angina.

The following factors are under discussion at present:

(1) *Effect on the β_1-receptors in the heart*

Beta-blockers reduce heart rate and therefore reduce the work done by the heart muscle. This allows a longer period for diastolic filling time. They also reduce the rise of blood pressure on exercise, the velocity of myocardial contraction and oxygen consumption for any given work load (Taylor, 1973). Furthermore, internal shunting appears to occur in the coronary circulation after blocking the β_1-receptors so that blood flow to an ischaemic area is maintained (Pitt and Craven, 1970).

(2) *Relevance of the other properties of the β-blockers*

It seems that the therapeutic value of the β-blockers lies with the β-blocking activity and apparently not with the various other properties such as the membrane stabilising and intrinsic sympathomimetic actions. Glyceryl trinitrate appears to relieve the pain in angina by reducing the pulse-rate product, which is the figure produced by multiplying the systolic blood pressure by the heart rate.

As propranolol, oxprenolol, practolol, and sotolol all depress the pulse-rate product by about 20 per cent, the β-blockers probably do not rely on their membrane stabilising, intrinsic sympathomimetic, or cardioselective properties to achieve their therapeutic action in angina, since all these four agents differ widely in their respective pharmacological properties, as shown in table 1 (Prichard *et al.*, 1971).

Choice of beta-blocker in treating angina

It seems that all the available β-blockers are equally effective in the relief of pain in angina. In particular, Prichard *et al.* (1970) showed that propranolol, pindolol, oxprenolol, and sotolol have little to choose between them, whilst other trials have suggested that practolol is less effective (Prichard *et al.*, 1971). More recent studies have suggested that the newer β-blocking agents tolamolol and atenolol are at least as good as propranolol in the treatment of angina.

However, trials must involve optimum doses and, since the dose of β-blocker that can be tolerated varies considerably between different individuals, any fair comparison requires a variable dose comparative trial. It is for this reason that at present no fair comparison can be made between the currently available β-blockers.

Selecting patients with angina for treatment with beta-blockers

All patients with angina should respond to treatment with β-blockers and failure to do so may indicate misdiagnosis (Amersterdam *et al.*, 1969). However, on theoretical grounds the following patients should especially benefit from their use:

(1) Patients with a high degree of emotionally-induced angina,

(2) Patients with high plasma lipids and free fatty acids,

(3) Patients who are taking large amounts of other drugs which are used to reduce the pain of angina. Beta-blocking agents will allow a reduction in the number of glyceryl trinitrate tablets (Roy *et al.*, 1975) and isosorbide tablets (Russek, 1968) taken by patients with angina.

Use of the beta-blocking agents

There are several general principles which should be observed when prescribing any of the β-blockers:

(1) Small initial dose

(a) The most dramatic change in the sympathetic environment of the heart seems to take place at the beginning of treatment with the first few doses. The greatest danger of precipitating heart failure is therefore at the very beginning of treatment.

(b) Response to any of the β-blockers can be surprisingly rapid especially in the hypotensive effect.

For these two reasons treatment should begin with a low dose and after the initial response the drug dosage may be increased progressively until the optimum effect is achieved, which may involve surprisingly large doses (Hart, 1975).

(2) Patients with bradycardia

Beta-blockers should not be used in patients with heart block or sinus bradycardia as further reduction of the heart rate via β_1-blockade may well precipitate cardiac failure and attacks of angina. In general, β-blockers should not be given to patients with pulse rates of 60 per minute or less.

(3) Patients with airflow obstruction and cardiac insufficiency

In view of the β_2-blocking effect, beta-blockers should not be given to patients with histories of:

(a) Chronic airflow obstruction,

(b) Asthma,

(c) Cardiac failure.

However, if beta-blockers are especially indicated in these types of patient, it appears that those agents which possess intrinsic sympathomimetic action are less likely to precipitate cardiac failure or bronchoconstriction.

TABLE 2

RELATIVE DOSAGE SCHEMES AND PRICES OF THE AVAILABLE β-BLOCKERS

		Hypertension		*Angina pectoris*	
Beta-blocker	*Tablet size in mg & *price per 100*	*Initial dose*	*Average maintenance dose*	*Initial dose*	*Average maintenance dose*
ACEBUTOLOL 'Sectral'	100 £3·50	not promoted for hypertension		200 mg bd	200–300 mg tds
METOPROLOL 'Lopressor' 'Betaloc'	50 £3·50 100 £6·50	100 mg bd	100–200 mg bd	50–100 mg tds	50–100 mg tds
OXPRENOLOL 'Trasicor'	20 £2·16 40 £3·54 80 £5·40 160 £9·74	80 mg bd	160–320 mg tds	40 mg tds	40–160 mg tds
PINDOLOL 'Visken'	5 £4·58	5 mg bd/tds	5–15 mg tds	2·5–5 mg bd	2·5–5 mg tds
PRACTOLOL 'Eraldin'	100 £3·55	100 mg bd	100–600 mg tds	100–200 mg bd	100–300 mg tds
PROPRANOLOL 'Inderal'	10 £1·10 40 £2·10 80 £4·20	40 mg tds	80–160 mg tds	40 mg tds	40–160 mg tds
SOTOLOL 'Betacardone' 'Sotocor'	40 £2·90 80 £4·35	80 mg bd/tds	80–200 mg tds	80 mg bd	80–160 mg tds
TIMOLOL 'Blocadren'	10 £4·00	5 mg tds	10–15 mg tds	5 mg tds	5–15 mg tds

*Prices quoted at June 1975

Furthermore, the so-called cardioselective β-blockers (i.e. practolol, acebutolol, tolamolol, atenolol, and metoprolol) should theoretically have little effect on the β^2-receptors in the bronchi. In practice, however, patients with airflow obstruction are not fully protected and the cardioselective β-blockers should be used with extreme caution, if at all, in such patients.

(4) Maximum dose tolerated

In angina, the maximum dose of β-blocker which can be tolerated should be used to achieve the greatest benefit to the patient (Prichard and Gillam, 1971).

(5) Frequency of administration

Each individual β-blocker has its own physiological and pharmacological half-life and, therefore, in order to obtain the optimum effect in both hypertension and angina the frequency of administration should be aimed at maintaining a continuous, optimum plasma level.

A guide to dosage regimens for all the available beta-blockers is given in table 2.

Side-effects of the beta-blocking agents

Many side-effects have been reported in patients taking β-blockers and the following are some of the more clinically important:

(1) Cardiac failure

Although this side-effect is uncommon in normal practice, when it occurs it is generally severe. Prichard and Gillam (1969) showed that the risk of inducing heart failure is greatest at the beginning of treatment and this is one reason for starting with a small initial dose. The reported incidence of this occurring varies from 1:20 (O'Brien and MacKinnon, 1972) to 1:300 (Zacharias *et al.*, 1972) and would be even less if the β-blocker is combined with a diuretic or even digoxin in those patients potentially at risk.

(2) Side-effects in the central nervous system

A number of different side-effects have been reported affecting the C.N.S. in people taking β-blockers.

(a) *Depression.* Several reports have been made of depression after treatment with propranolol and in one study two patients, admittedly with previous mental instability, committed suicide (Waal, 1967). Other β-blockers have also been noted to be associated with depression and lethargy in those people taking the drug (Morgan *et al.*, 1972); the frequency is about 1:25.

(b) *Hallucinations.* Although these are quite uncommon (about 1:80) they are disturbing to patients when they do occur (Zacharias *et al.*, 1972).

(c) *Dreams.* These are far more common and the incidence has been suggested to be as high as 1:30 in patients taking propranolol (Tarazi and Dustan, 1972). However, Morgan *et al.*, (1972) found that about half their patients taking pindolol had frequent and often bizarre dreams whereas a much smaller incidence has been noted in patients taking practolol and oxprenolol (Prichard, 1970).

(d) *Insomnia.* Prichard and Gillam (1969) reported two per cent of their patients taking propranolol had difficulty with sleeping and Zacharias *et al.* (1972) has suggested that the incidence is only one per cent. Other β-blockers have also been noted to cause insomnia and again the incidence is low.

It seems logical, therefore, to omit the evening dose in any patient who gives a history of dreams, hallucinations, or insomnia when taking β-blocking agents.

(3) Effects on the peripheral circulation

Beta-blockade will reduce blood flow through the blood vessels of muscles but not, in theory, through those of the skin. However, Raynaud's phenomenon has been reported in one study with propranolol, oxprenolol, and pindolol in four per cent of the subjects (Tarazi and Dunstan, 1972).

(4) Weight gain

Various reports (e.g. Seedat and Stewart-Wynne, 1972) have shown that treatment with β-blockers can lead to an increase in weight of one to two kilograms.

(5) Miscellaneous side-effects

Apart from the above major side-effects a number of minor and much less serious problems have been reported with all the available beta-blockers. Gastro-intestinal upsets, especially discomfort and diarrhoea can occur with any of the agents, but seem to be more common with high doses of practolol.

Muscle cramps are not uncommon with pindolol but have also been noted in patients taking practolol (Prichard, 1970). The syndrome has been noted of systemic lupus erythematosus after practolol and responds to withdrawal of the drug and the addition of corticosteroids (Raftery and Denman, 1973).

Finally, reduced libido has been reported in a small number of people taking propranolol and pindolol (Prichard and Gillam, 1969). In general, of course, the β-blockers abolish impotence in patients made impotent by other antihypertensive agents.

(6) Special side-effects of practolol

Recent reports have suggested that long-term use of practolol can be associated with various types of skin rashes, ocular damage, and sclerosing peritonitis. Felix *et al.* (1974) reported rashes ranging from eczema and lichen planus-like rashes to highly characteristic toxic psoriasiform eruptions in 21 patients taking practolol. Three of these patients also had ocular damage, including ectropion and corneal ulceration which appeared to be permanent.

Because of these severe effects of long-term treatment with practolol, its use has now been reserved only for those patients in hospital who might gain special benefit from it.

Conclusion

From what has been said it seems that at present there is little to choose between the available β-blocking agents in the treatment of both hypertension and angina. All of them seem to be equally effective with the possible exception of practolol.

The relevance of the various additional properties of the β-blockers is still clinically uncertain. Until further trials have proved the particular superiority of one or more of the different β-blockers it seems that the clinician must be guided by the comparative cost as well as the comparative degree of side-effects.

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